Impact of Intermittent Screening and Treatment for Malaria among School Children in Kenya

A Cluster Randomized Trial

Katherine E. Halliday
George Okello
Elizabeth L. Turner
Kiambo Njagi
Carlos Mcharo
Juddy Kengo
Elizabeth Allen
Margaret M. Dubeck
Matthew C.H. Jukes
Simon J. Brooker

The World Bank
Africa Region
Health Unit
&
Development Research Group
Impact Evaluation Team
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Abstract

This paper investigates the effects of intermittent screening and treatment of malaria on the health and education of school children in an area of low-to-moderate malaria transmission. A cluster randomized trial was implemented with 5,233 children in 101 government primary schools on the south coast of Kenya in 2010–12. The intervention was delivered to children randomly selected from classes 1 and 5 who were followed up twice across 24 months. Once during each school term, public health workers used malaria rapid diagnostic tests to screen the children. Children who tested positive were treated with a six-dose regimen of artemether-lumefantrine. Given the nature of the intervention, the trial was not blinded. The primary outcomes were anemia and sustained attention and the secondary outcomes were malaria parasitaemia and educational achievement. The data were analyzed on an intention-to-treat basis. Anemia in this setting in Kenya, intermittent screening and treatment, as implemented in this study, is not effective in improving the health or education of school children. Possible reasons for the absence of an impact are the marked geographical heterogeneity in transmission, the rapid rate of reinfection following artemether-lumefantrine treatment, the variable reliability of malaria rapid diagnostic tests, and the relative contribution of malaria to the etiology of anemia in this setting.

This paper is a joint product of the Health Unit, Africa Region; and the Impact Evaluation Team, Development Research Group. It is part of a larger effort by the World Bank to provide open access to its research and make a contribution to development policy discussions around the world. Policy Research Working Papers are also posted on the Web at http://econ.worldbank.org. The authors may be contacted at katherine.halliday@lshtm.ac.uk

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Impact of intermittent screening and treatment for malaria among school children in Kenya: a cluster randomized trial

Katherine E. Halliday, George Okello, Elizabeth L. Turner, Kiambo Njagi, Carlos Mcharo, Juddy Kengo, Elizabeth Allen, Margaret M. Dubeck, Matthew C.H. Jukes & Simon J. Brooker

1. Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, UK
2. Health Systems and Social Science Research Group, Kenya Medical Research Institute-Wellcome Trust Research Programme, Kilifi, Kenya
3. Department of Biostatistics and Bioinformatics and Duke Global Health Institute, Duke University, Durham, North Carolina, United States of America.
4. Division of Malaria Control, Ministry of Public Health & Sanitation, Nairobi, Kenya.
5. Health and Literacy Intervention Project, Ukunda, Kenya
6. Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, UK
7. Department of Teacher Education, College of Charleston, South Carolina, United States of America
8. Graduate School of Education, Harvard University, Cambridge, Massachusetts, United States of America
9. Malaria Public Health Department, Kenya Medical Research Institute-Wellcome Trust Research Programme, Nairobi, Kenya

*Corresponding author: Katherine E. Halliday  Email address: katherine.halliday@lshtm.ac.uk

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Keywords: malaria, Plasmodium falciparum, intermittent screening and treatment, schools, artemether-lumefantrine, Africa

Trial registration. This trial was registered at Clinical Trials.gov. Identifier: NCT00878007 http://www.clinicaltrials.gov/ct2/show/NCT00878007?term=NCT00878007&rank=1
### Abbreviations

| Abbreviation | Description                                      |
|--------------|--------------------------------------------------|
| Adj.MD      | Adjusted mean difference                         |
| Adj.RR      | Adjusted risk ratio                              |
| AL          | Artemether Lumefantrine                          |
| CV          | Coefficient of variation                         |
| GEE         | Generalized estimating equations                 |
| Hb          | Hemoglobin                                       |
| ICC         | Intraclass correlation coefficient                |
| IPT         | Intermittent Preventive Treatment                |
| IQR         | Inter-quartile range                             |
| IST         | Intermittent Screening and Treatment             |
| *P.falciparum* | *Plasmodium falciparum*                     |
| PCR         | Polymerase chain reaction                        |
| RDT         | Rapid diagnostic test                            |
| SD          | Standard deviation                               |
| SES         | Socioeconomic status                             |
Introduction

In many malaria endemic countries, successful control programs have recently reduced the level of malaria transmission [1-3] and as a consequence, immunity to malaria is acquired more slowly and the burden of clinical malaria is shifting from the very young to older children [4,5]. Recent success in malaria control has also prompted a renewed emphasis on malaria elimination, leading to a shift in focus from targeting only clinical malaria to also identifying and treating asymptomatic malaria parasitaemia [1,6]. Infection rates are typically highest among school-aged children [7,8] who, due to recent improvements in primary school access, are increasingly enrolled in school [9,10]. Tackling such parasitaemia, whether or not it results in clinical disease, is important for two reasons. First, an increasing body of evidence is showing that chronic untreated *Plasmodium* infections can negatively affect children’s health [11,12] and cognitive function [13-15], including sustained attention [16] and ultimately, their educational achievement [17,18]. Second, with the move towards elimination in low-moderate transmission settings [19,20], there is a need to tackle untreated reservoirs of infection, to which school children are important contributors [21,22]. Yet, surprisingly, there remains a lack of consistent policy and technical guidance [23] on which interventions can reduce the burden of malaria among school children and which can cost-effectively be delivered through existing school systems.

Previous studies have highlighted the beneficial impact of school-based intermittent preventive treatment (IPT) on health and cognitive function in high [24] and high, seasonal [25] malaria transmission settings. However, the recent withdrawal of the primary drugs for IPT, sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ), in many East African countries precluded further investigation of IPT using SP+AQ. A possible alternative to IPT is intermittent screening and treatment (IST), whereby individuals are periodically screened for *Plasmodium* infection using a rapid diagnostic test (RDT) and those infected (whether symptomatic or not) are treated with a full course of first-line drug treatment, artemether-lumefantrine (AL). The potential of IST was first highlighted by modeling work, [26,27] and its comparable efficacy to IPT in antenatal care [28] has been evaluated, although a recent trial in Burkina Faso indicated no impact of IST on community-wide malaria transmission [29]. This paper reports the results of a cluster randomized trial investigating the impact of IST in schools on health and education outcomes in school children in a low-moderate transmission setting on the south coast of Kenya [30].

Methods

The original protocol for the trial (Protocol S1) and the supporting CONSORT checklist (Checklist S1) are provided as supporting information. Trial instruments and data are available on the World Bank Microdata catalogue at: http://microdata.worldbank.org/index.php/catalog/671.

Ethics Statement

The study was approved by the Kenya Medical Research Institute and National Ethics Review Committee (SSC No. 1543), the London School of Hygiene & Tropical Medicine Ethics Committee (5503), and the Harvard University Committee on the Use of Human Subjects in Research (F17578-101). Prior to the randomization, meetings were held with community and school leaders and parents/guardians in each school to explain the study objectives and procedures. Parents/guardians of
all children in class 1 and 5 were requested to provide individual written informed consent and they were given the option to withdraw their child from the study at any time. Prior to every IST round or assessment the procedures were explained to the children and they were required to provide verbal assent. An independent data monitoring committee reviewed the trial protocol, data analysis plan and preliminary results.

**Study area and population**

The trial was conducted from January 2010 to March 2012 in Kwale and Msambweni districts on the south Kenyan coast (Figure 1). Malaria transmission in the area is low to moderate and perennial with seasonal peaks following the two rainy seasons (April-July and September-November) [31]. The primary malaria vectors are *Anopheles gambiae s.l.* and *Anopheles funestus* [32,33]. Intensity of malaria transmission has been declining in recent years: school surveys conducted in 2010 reported prevalences of *P. falciparum* of 9-24% [34,35], compared to 64% in 1998 [32]. Overall reported net use in the region is high, with the communities having benefited from universal coverage campaigns. During the two-year trial period, albendazole was delivered through households as part of the National lymphatic filariasis campaign in 2011, although coverage was not extensive and Praziquantel was delivered schools in the area in June 2011. The vast majority of the population in these districts belong to the Mijikenda ethnic group, with Digo and Duruma the predominant subgroups [36]. The region is primarily rural with subsistence farming of maize and cassava practiced by many of the communities, although titanium mining has recently become an important source of employment. In economic and educational terms, the districts are ranked the seventh poorest in Kenya and consistently have some of the worst performing schools in the national school examinations [37].

Kwale District has 85 schools across four zones, and in two of these an alternative literacy intervention study was underway. Therefore only 20 schools from Mkongani and Shimba Hills zones were included in our study, allowing the two interventions to proceed without leakage. In Msambweni District 81 of the 112 schools were selected, with schools in Lunga Lunga and Mwereni zones greater than 70 km away from the project office excluded because of logistical considerations in visiting them.

**Study design**

The study was designed as a factorial cluster randomized trial to investigate the impact of two interventions: (i) the impact of school-based IST of malaria on the health, sustained attention and education of school children, and (ii) the impact of a literacy intervention on education. In order to evaluate the potential interaction between the two interventions, schools were randomized to one of four groups, receiving either: (i) IST alone; (ii) the literacy intervention alone; (iii) both interventions combined; or (iv) control group where neither intervention was implemented (Figure 2). The study was not blinded. Due to the factorial design of the trial and lack of interaction detected (interaction effect p-values of 0.45, 0.26 and 0.60 for the three key literacy outcomes) between the two interventions in class 1 where both were implemented, we report the results of the interventions separately. Only the IST intervention results are reported in this paper. The results of the literacy intervention will be reported in a separate paper.
targeting an education research audience as the literacy intervention was focused purely on enhanced English and Swahili literacy instruction and was not intended to have an impact on health.

Recruitment and baseline sample collection were conducted in January-March 2010 using children randomly selected from classes 1 (age range: 5-15 years) and 5 (age range: 8-20 years). Both classes received the IST intervention, but the literacy intervention was targeted only to children in class 1 and as they advanced to class 2, as it focused on the initial stages of literacy acquisition. Education outcome measures were assessed in the same children at 9 and 24 months and health outcome measures at 12 and 24 months. Full details of the eligibility, randomization, intervention procedures and baseline results have been presented elsewhere [30,35]. The study is registered with ClinicalTrials.gov, NCT00878007.

**Sample size**

The sample size was based on methods designed for cluster-randomized trials and assumed that 101 eligible schools would be randomized to the four intervention groups, with an average of 50 children per school. On the basis of data collected previously in the study area, the baseline prevalence of anemia was assumed to be 20% and the coefficient of variation (CV) 0.2 [30]. In order to detect a 25% reduction in the prevalence of anemia between the two groups, based on previous work in Kenya [24], the sample size required to give a study with a power of 80% at a two-sided significance level of 5%, was a total of 27 schools in each arm with 50 children per school. A sample size of 101 schools with 25 children per class (i.e analyzing classes 1 and 5 separately), would enable us to detect, with 80% power and 5% significance, an approximate difference of 0.2 standard deviations between arms of the trial in educational achievement (assuming an intra-class correlation coefficient (ICC) of 0.2 and a pre-post correlation of 0.7), and a difference of approximately 0.15 SD in tests of sustained attention (assuming an ICC of 0.1 and a pre post correlation of 0.7) [24]. The increased number of schools required for the sustained attention and educational achievement outcomes provided greater power (97%) to detect a 25% reduction in the prevalence of anemia, or alternatively 85% power to detect a 20% reduction.

**Randomization**

The 101 schools were randomized in two stages (Figure 2), with each stage conducted during a public ceremony. In Kenya, schools are aggregated into sets of between three and six closely located schools, which regularly meet and share information, supported by a Ministry of Education Teacher Advisory Centre tutor. Our 101 study schools formed 24 of these sets of schools, which were randomized either to receive the literacy intervention or to serve as the literacy control. Randomization of these sets of schools was stratified by (i) set size, to ensure equal numbers of schools in the experimental groups; and (ii) average primary school leaving exam scores of the school sets, to balance the two study groups for school achievement. This randomization procedure was designed to minimize contamination of the literacy intervention methods across the study groups. In stage two, the IST intervention was randomly allocated at the level of the school, with the 101 schools re-stratified by (i) literacy intervention group assignment and (ii) quintiles of average school exam scores, producing ten strata overall.

**Enrollment**
At enrollment, children’s height and weight were measured, axillary temperature was digitally recorded, and finger-prick blood samples were obtained to prepare thin and thick blood films and to determine hemoglobin concentration (Hb). Children known or suspected to be homozygous for sickle cell trait or pregnant were excluded. Any child found with a hemoglobin concentration <80g/L was referred by the nurse to the nearest health facility for iron therapy, and any child found with Hb <50g/L was taken to the hospital for transfusion. Baseline parasitaemia was measured in the intervention group during the first round of screening but was not measured in the control group owing to the ethical constraints of testing for malaria but not treating children found to be infected in the control schools, which was of particular importance at baseline as the intervention involved screening of Plasmodium infection.

A questionnaire was administered to parents/guardians to record information on residence, family size, ownership of possessions, mosquito net use by them and their children, recent deworming of the child, house construction and parental education level.

**Intervention**

IST was outlined as a possible strategy in the “Malaria-Free Schools Initiative”, as part of the Kenya National Malaria Strategy 2009-2017 [38]. During IST, children were screened once a school term for malaria parasitaemia using an RDT (ParaCheck-Pf device, Orchid Biomedical Systems, Goa, India) which is able to detect *P. falciparum*. Screening was conducted by laboratory technicians. Repeat visits were made to follow-up children absent on the day of screening. Children (with or without malaria symptoms) found to be RDT-positive were treated with a six dose regimen of artemether-lumefantrine (AL) (artemether 20 mg/lumefantrine 120 mg, Coartem®, Novartis) over three days. Doses of AL were based on weight, with children stratified into one of the four categories (<15 kg, 15-24.9 kg, 25-34.9 kg, and ≥35 kg). AL was given at a dose of 20/120 mg to children <15 kg, 40/240 mg to children 15-24.9 kg, 60/360 mg to children 25-34.9 kg, and 80/480 mg to those who weighed ≥35 kg. Parents or older siblings of children were called and a nurse explained that their child was infected with malaria parasites and required treatment. Doses 1, 3 and 5 were given under direct observation at the school by the study nurses. Children were given milk and biscuits with the AL and observed for 30 minutes after drug administration. If vomiting occurred during this period, drugs were re-administered. If vomiting occurred on a second occasion, this was noted but the drugs were not given again. Such children were not excluded from the trial and they were eligible to receive drugs on the subsequent two days. The parents/older siblings or study children themselves if in the older classes were given doses 2, 4 and 6 each day for evening administration and provided with instructions on treatment. Children absent from school on days two or three of treatment were followed up at their home by the nurse, and provided with the doses. Supervised treatment was defined as nurses administering and directly observing doses 1, 3 and 5 taken on three consecutive mornings in the school and recording doses 2 and 4 reported by the child as having been taken the previous evenings. No direct confirmation of whether dose 6 was taken was recorded by the nurse. The record of supervised treatment was used as a proxy for compliance. Five rounds of screening and treatment were implemented. The first round was conducted alongside baseline health assessments in March 2010, the second round in July 2010, the third in September 2010, the fourth in March 2011 and the final round in October 2011.
Adverse events were monitored by the study team for 24 hours after each treatment, and a further 28 days thereafter using a passive surveillance system in schools. Travel costs were reimbursed and treatment charges waived. Adverse experiences were monitored until the event was cured or had stabilized. Agranulocytosis and hepatotoxicity were not assessed because of logistical constraints.

**Follow-up**

Cross sectional health surveys were carried out at 12 and 24 months. During these surveys, temperature, weight and height were measured and a finger prick blood sample was collected for determination of malaria parasitaemia and Hb. Children with an axillary temperature ≥37.5°C were tested using a RDT, providing an on-the-spot diagnosis for malaria and treatment was administered as per national guidelines.

**Laboratory methods**

Hb was measured using a portable hemoglobinometer (Hemocue, Ängelholm, Sweden). Thick and thin blood films were stained with Giemsa, asexual parasites were counted against 200 white blood cells (WBCs), and parasite density was estimated assuming an average WBC count of 8000 cells/µL. A smear was considered negative after reviewing 100 high-powered fields. Thin blood smears were reviewed for species identification. All blood slides were read independently by two microscopists who were blinded to group allocation. Discrepant results were resolved by a third microscopist.

**Attention and educational achievement**

Tests of sustained attention and educational achievement were administered at baseline, 9 months and 24 months. Sustained attention was a primary outcome, assessed through the code transmission test, adapted from the TEA-Ch (Tests of everyday attention for children) battery [39]. A recorded list of digits is read aloud and children are required to listen for a code – two consecutive occurrences of the number 5 - and then record the number(s) that preceded the code. To avoid floor effects, a simpler measure of sustained attention - the pencil tap test [40] - was used at baseline for the younger cohort. Children were required to tap a pencil on the desk a predetermined number of times in response to the assessor’s taps. The secondary outcome of educational achievement was measured through tests of literacy and numeracy. Literacy was assessed through group administered English spelling tests, adapted from PALS (Phonological Awareness Literacy Screening) [41], with the younger classes asked to spell five 3-letter words and credit given for phonetically acceptable choices for each letter and the older classes asked to spell 25 words with credit given for correctly spelling the features and sound combinations of the word. Numeracy assessments involved an oral test of basic arithmetic for younger children at baseline and 9 month follow-up and written arithmetic at 24 month follow-up and a written arithmetic test throughout for older children. All educational assessments were piloted in schools situated outside of the study area prior to use in the baseline and follow-up evaluations. During piloting the assessments were conducted under the same assessment conditions on two occasions a week apart, with the correlation between the scores at the two time points providing a reliability score. The inclusion criteria for the tests used in this
trial was a Cronbach’s alpha correlation of 0.7 or above, indicating a well-constructed test with consistent administration.

The educational assessments were conducted separately to the health assessment both for logistical reasons and so as not to cause bias during the educational assessments due to apprehension of the finger-prick. The education assessments preceded the latter by an average of a week at baseline and 24 month follow-up. However, during the first follow-up, the education assessments were conducted at the end of the school year (9 months) and the health assessments were conducted at end of a full year (12 months).

**Data analysis**

Data were double-entered, consistency checks were performed and all analysis was conducted using Stata software version 12.1. The pre-specified primary outcome measures were the prevalence of anemia, defined according to age and sex corrected World Health Organization (WHO) thresholds: hemoglobin concentration <110g/l in children under 5 years; <115g/l in children 5 to 11 years; <120g/l in females 12 years and over and males 12 to 15 years old; and <130g/l in males over 15 years, with no adjustment made for altitude [42] and sustained attention. The pre-specified secondary outcomes were the prevalence of *P.falciparum* and scores for spelling and arithmetic. Reported information on ownership of household assets and household construction was used to construct wealth indices using principal component analysis [43] and resulting scores were divided into quintiles. Anthropometric measurements were processed using the WHO Anthroplus Stata macro [44] to derive indicators of stunting, thinness and underweight.

The analyses described here correspond to a pre-specified statistical analysis plan, approved by both the data monitoring committee and trial steering committee before any data were examined.

Baseline school and child characteristics, together with baseline measurements of the study outcomes were summarized by study groups separately, with class-specific study outcomes reported separately by class. Counts and percentages were used for categorical variables. Means and standard deviations, or medians and the limits of the inter-quartile range were reported for continuous variables. Coefficients of variation (CVs) for the binary (health) outcomes and intraclass correlation coefficients (ICCs) for the continuous (cognitive and education) outcomes were calculated from the baseline measures using appropriate formulae [45].

The effectiveness of the IST intervention was assessed using generalized estimating equations (GEE) with robust standard errors and an exchangeable correlation matrix to allow for clustering within schools. All main analyses used the intention-to-treat principle whereby children were analyzed in the intervention group that they were assigned to, even if the child moved schools or did not fully comply. The primary pre-specified analysis adjusted for age (as a continuous variable), sex and the baseline measure of the outcome, except for baseline *P.falciparum*, which was not measured in the control schools. As randomization of schools to the IST intervention was stratified based on both literacy intervention
assignment and school mean exam score (Figure 2), all adjusted analyses presented account for these two stratification factors. Data for classes 1 and 5 combined were used for the health outcome analyses. However, as different assessments were administered for classes 1 and 5 for the evaluation of attention (e.g. pencil tap for class 1 and code transmission for class 5), literacy and numeracy outcomes, analyses were conducted for each class separately. Separate GEE analyses were conducted for the first and second follow-ups. No formal adjustment was made for multiple testing therefore p-values should be interpreted with due caution. However as specified in the statistical analysis plan formal testing was restricted to two primary and three secondary pre-specified outcomes.

For comparison purposes, we also obtained estimates from an unadjusted model that did not adjust for baseline outcome measures, child characteristics or study design (literacy group and mean school-exam score) and hence retained all study children assessed at follow-up regardless of whether they had baseline measures. Secondary analyses were conducted additionally adjusting for stunting, school-feeding program and SES on top of the pre-specified variables. These additional adjustments had no notable impact on the effect estimates and are not presented.

In order to gain power and account for missing data, random effects models, using a likelihood-based approach were fitted to the one-year and two-year follow-up data simultaneously (Tables S1, S2, S3, S4, S5, S6 and S7; Text S1). Additional sensitivity analyses were conducted to examine intervention effects when children who had transferred from their original school were excluded from the analyses (Table S8).

Role of the funding source
The funders had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Trial profile and baseline data
One hundred and one schools were randomized to one of the two study groups (Figure 3). In total, 7,337 children aged between 5 and 20 years (median: 10 years and IQR: 8-13 years) were randomly selected in January 2010 of which 5,772 (78.7%) parents consented, with no real differences found between groups in terms of percentage of parents refusing and not attending the meetings. Overall, 5,233 children were initially enrolled, of which 5,176 (98.9%) children were eligible for follow-up after the baseline assessments. Characteristics of the children included in each of the study groups are shown in Table 1. The numbers of children per school ranged from 18 to 58 but overall were well balanced between groups (control: median, 52 inter-quartile range [IQR], 50-54 and intervention: median, 53 IQR, 50-55). A difference in percentage of children unavailable for the baseline health surveys was observed between the groups with 5.1% and 10.1% unavailable in the control and intervention groups respectively (Figure 3).
Children in the two study groups were broadly similar in regard to age, sex, anthropometric indices, bed-net use, and household characteristics, with some slight apparent differences in school size and socioeconomic status (Table 1). The primary outcomes, anemia and educational measures were also similar between groups at baseline, anemia prevalence was 45.2% and 45.5% in control and intervention groups respectively. The prevalence of *P. falciparum*, assessed only in the intervention group at baseline, was 12.9%.

**Compliance with screening and treatment**

During the 24 months of intervention, an average of 2,340 children (88.4% of eligible study children) in the 51 intervention schools were screened at each visit, of whom, on average 17.5% were RDT-positive (Table 2). Of the study children, 84.0% were screened at four or more IST rounds and 66.8% were screened at all five rounds. By the fifth screening round, 3.3% children were lost due to withdrawal or death and a further 17.7% of children were lost due to out-migration. The percentage of children RDT-positive at each screening ranged from 14.9% to 19.2%, with no distinct trend over time. Overall, 99.1% of RDT-positive results led to treatment across the five screening rounds and 92.6% of these were recorded as receiving the fully supervised six-dose treatment regime, (Table 2). There was an apparent decline in full supervision (a proxy for compliance) with time, falling from 96.9% at the first round to 81.7% at the fifth round. RDT performance, examined against a “gold standard” of expert microscopy, revealed consistently high specificity, greater than 90% at all rounds, whereas sensitivity was more variable ranging from 68.7% to 94.6% across surveys, with higher sensitivity observed during the wet season compared to the dry season (Table 2).

**Follow-up**

Of the 5,233 children enrolled initially, 4,446 (85.0%) were included in the 12 month follow-up health survey and 4201 (80.3%) were included in the 24 month health survey (Figure 3). At 12 and 24 months, children lost to follow-up across both study arms were largely similar to children followed up (Tables S1 and S2) with slightly lower spelling scores in those children lost to follow-up across both groups and a higher proportion of children whose parents had no schooling in those lost to follow-up in the intervention schools. The prevalence of *P. falciparum*, in the intervention group, was lower in children lost to follow-up (8.6%) compared to those followed-up (13.6%) at both 12 and 24 months.

Overall, 4,656 (89.0%) of children were included in the 9 month follow-up education survey and 4,106 (78.5%) in the 24 month follow-up survey. Children unavailable for the follow-up educational surveys at 9 and 24 months were similar across the two study groups (Tables S4 and S5), with a slight imbalance in SES and parental education categories seen between children available and unavailable for the survey in the intervention group. Additionally baseline prevalence of *P. falciparum* was lower in children lost to follow-up (9.1%) compared to those followed-up (13.3%) in the intervention arm.

As intention-to-treat analysis was performed, no adjustment was made for children transferring between schools and study groups at the follow-ups. Overall, 308 children were recorded as transferred by the
end of the study. Of those, 46 (0.9%), 71 (1.8%) and 308 (5.9%) children were assessed in a different school from their initial enrollment school, at 9-month, 12-month and 24-month follow-ups, respectively. Sensitivity analysis excluding these transfers resulted in no change in direction or magnitude of results (Table S8).

**Effect of IST on anemia and *P. falciparum* infection**

At 12 months follow-up, 2,148 children in the control schools and 2,298 in the intervention schools provided a finger-prick blood sample for Hb assessment, and at 24 months 2,027 and 2,174 children provided finger prick samples in the control and intervention groups respectively. There was no significant difference in the prevalence of anemia between children in the two groups at 12 or 24 month follow-ups (Adjusted risk ratio (Adj.RR): 1.03, 95%CIs: 0.93, 1.13 p=0.621 and Adj.RR: 1.00, 95%CIs: 0.90, 1.11 p=0.953) respectively (Table 3); the same was observed in relation to mean Hb. There was also no significant difference in the prevalence of *P. falciparum* between study groups at 12 or 24 months. Subgroup analysis of the impact of IST intervention on anemia according to *Plasmodium* prevalence at baseline (using 12-month estimates for the control group as a proxy for baseline), demonstrated no differential impact by prevalence category (<5%, 5-19% and 20%+) at either follow-up. Similarly, no difference was seen when analysis was stratified, within the intervention group only, by numbers of treatments received across the study period (Tables S9 and S10).

**Effect of IST on attention and educational achievement**

At both 9- and 24-months follow-up, there was no statistical difference in mean scores for sustained attention between study groups in either class with Adjusted mean difference (MD): -0.44, 95%CIs: -1.09, 0.21 p=0.180 and Adj.MD: 0.28, 95%CIs: -0.23, 0.79 p=0.283 for classes 1 and 5 respectively at the 24 month follow-up (Table 4). Similarly there was no significant difference between groups on scores for spelling in the older class at 9 and 24 month follow-ups (Adj.MD: -0.31, 95%CIs: -1.26, 0.63 p=0.515 and Adj.MD: 0.71, 95%CIs: -0.34, 1.76 p=0.183) nor for arithmetic at either follow-up (Table 5). However, at 9-months follow-up, children in the younger class in the intervention group had lower mean adjusted scores for the spelling task and the same trend was observed at 24 months (Adj.MD: -0.65, 95%CI: -1.11, -0.20 p=0.005). Similarly at 24 months, in the younger class, children in the intervention group scored on average 0.60 points lower in the arithmetic assessments than children in the control group (Adj.MD: -0.60, 95%CI: -1.02, -0.19 p=0.005).

**Surveillance for adverse effects**

Active surveillance found that 4.5% (92/2030) children reported one or more adverse effects within 2 days of receiving treatment, including headache (68; 3.3%), stomach ache (38; 1.9%), dizziness (17; 0.8%), vomiting (7; 0.3%) and pruritis (10; 0.5%). During the 24 months of follow-up, 11 children died: 5 in the intervention group and 6 in the control group. Cause of death was investigated and included yellow fever, heart defect, leukemia, drowning, trauma, pneumonia and pediatric HIV. In the intervention group, none of these deaths occurred within 30 days of the screening and treatment and therefore were not attributed to the intervention.
Discussion
School-based malaria control is increasingly recognized as an important potential component for integrated school health packages [46]. However, as yet there is no consensus about the most effective malaria interventions for the alternative transmission settings. To our knowledge, we conducted the first cluster-randomized trial of the impact of school-based intermittent screening and treatment (IST) for malaria. We failed to detect any overall benefit of IST using AL on the health, attention or educational achievement of school children in this low-moderate malaria transmission setting.

The reasonably high follow-up rates of on average 87.0% and 79.4% at the first and second follow-ups respectively, equal between groups at each follow-up, suggest sample bias was not responsible for the lack of impact observed. The higher proportion of children unavailable for baseline health assessments was driven by a few initially apprehensive schools [47], which were subsequently assessed throughout the study and included in the unadjusted analyses. The differential baseline prevalence of \textit{P. falciparum} in those children available and unavailable for follow-up in the intervention group may reflect a higher proportion of withdrawal and absenteeism on screening and assessment days in schools in low transmission regions, where there was no treatment benefit. However, such a situation is unlikely to have masked any impact of IST as historical exposure and current parasite prevalence is highly predictive of subsequent malaria risk [48,49], and as such these children were less likely to have been infected and thus gain any potential benefit from treatment over the study period.

The absence of apparent differences between study groups in relation to either \textit{Plasmodium} infection or anemia at 12 or 24 months are contradictory to predictions from simulation analyses of mass screening and treatment in a moderate transmission setting [26,27]. One reason for these contrasting results may be the different coverage rates, where the simulations assumed 80% intervention coverage of the whole community in contrast to this study where the IST intervention covered two classes of the school populations only. In this low-moderate transmission setting less than 20% of children screened were eligible for treatment at each round. However, the lack of differential impact on anemia observed when schools were stratified by baseline prevalence of \textit{Plasmodium} infection (a proxy for transmission intensity) and by number of treatments received at the individual level, suggests there was no impact on long-term health even among the children receiving AL treatment.

A possible explanation for the lack of impact of IST on anemia at the group or individual level is high, localized, rates of re-infection and acquisition of new infections between screening rounds allowing no time for hematological recovery, indicated by the remarkably similar percentage of children RDT positive at each screening round. The use of AL may have contributed to rapid re-infection rates as it affords short (14-28 days) post-treatment protection [50,51]. Such a protection period would have provided extensive time at risk of acquiring new infections before the next round of IST at least three months later. A potential alternative would be dihydroartemisinin-piperaquine [52], which would afford a longer post-treatment prophylaxis period than AL between screening rounds, and has recently been successfully evaluated as part of IPT in Uganda [53]. Additionally, increased frequency of screening, six times a year as opposed to three could reduce the time at risk for parasite carriage and allow for hematological
recovery, but would be logistically and financially prohibitive. The marked, but stable heterogeneity of *Plasmodium* infection observed over the two years (school-level prevalence range: 0-75%) resulted in several schools experiencing no infection throughout all screening rounds, and a small sample of schools exhibiting repeatedly high proportions of RDT positive study children at each round. This heterogeneity, compounded by the large proportion of untested and therefore untreated asymptomatic carriers remaining in the communities likely led to study children in localized hotspots being exposed to high risk of infection immediately after treatment [20]. Analyses of the stability infection at both the school and the individual level, and the environmental correlates of such patterns, will be presented in a future paper.

The evaluation identified two further limitations of the IST approach. First, there was variability in RDT performance between screening rounds, with lowest RDT sensitivity during the dry season. However, diagnostic performance in this analysis was estimated assuming microscopy as a “gold standard”, and in light of concerns of the diagnostic accuracy of such reference tests, alternative methods of estimation for two or more malaria diagnostic tools in the absence of a “gold standard” have been suggested [54-56]. Additional analysis is underway to investigate diagnostic performance of RDTs and expert microscopy as well as the influence of individual, local transmission and seasonal factors during the two year study period. The recent study conducted in Burkina Faso failed to show a significant reduction in parasitaemia in the dry season following community-wide screening and treatment campaigns in the previous dry season [29], suggesting that screening and treatment with RDTs is not sensitive enough to reduce transmission even when delivered in a mass campaign. The use of PCR would constitute a more sensitive tool, additionally detecting subpatent infections which contribute to transmission [57-59], but would be operationally challenging. Second, there was a decline in supervised treatment over time, as it became logistically difficult for children who were absent on screening day and subsequently treated on a repeat visit, to be followed up on treatment day two and three by the nurse. Such children and/or their guardians and older siblings were given the full regimen with instructions on how to take the doses at home over the three days [60]. Altering the treatment supervision by the nurse from three days to the first day only would greatly reduce the cost of the IST intervention [61]. Although evidence indicates that unsupervised treatment is as effective at clearing parasitaemia as fully supervised treatment in clinical cases [62], unsupervised compliance may be lower when treating asymptomatic infection. Low efficacy of AL in the study is possible. No specific treatment efficacy evaluation was performed during this trial, however although there is mixed evidence as to whether there is a slight decline in efficacy of AL in Kenya [63,64] overall treatment success is thought to remain reasonably high.

In a region such as coastal Kenya, where food security is particularly low [65,66] and malaria transmission is low-moderate, it is probable that factors such as long term nutritional status, short-term access to food and helminth infections are stronger contributors to the etiology of anemia in this setting [67] than parasitaemia. These factors would result in a limited impact on anemia through a program targeting malaria only, rather than a package containing a combination of school-feeding, deworming and malaria control. This study thus contrasts with the previous IPT study conducted in Nyanza province, Kenya, [24], where malaria is predicted to be the greatest contributor to anemia [67], enabling a malaria control program to have a large impact on anemia directly.
Our finding of no significant differences between groups for sustained attention in either the younger or older classes at either follow-up is consistent with expectations, based on the lack of effect of IST on the assumed mediator, health. Likewise with the adjusted literacy and numeracy scores in the older class at both follow-ups, no significant differences between groups were found. However, in the younger class, at both 9 and 24 months, there was an apparent negative effect of the IST intervention on literacy scores and on arithmetic scores at 24 months. This seemingly negative impact of IST was found only in the younger class, where the literacy intervention was implemented. As no statistical interaction between the two interventions was detected in the younger class, the differences between study groups cannot be attributed to an effect of the literacy intervention. Because of the multiple tests conducted, this finding could be due to chance. If we were to use a highly conservative Bonferroni correction for the 16 tests (two health and six education outcomes, all at two follow-ups) from adjusted models, the apparent negative effects on spelling and arithmetic would lie close to the updated significance level. Alternatively these findings could demonstrate a negative effect of the by-term screening, involving an uncomfortable finger prick [68], with the intervention group experiencing increased apprehension of the finger prick during the education assessments as they associated the presence of our research team with the IST process [47], or reduced classroom attendance throughout the year in this group to avoid the IST intervention, or a combination. However, attendance measured at health and education assessment visits indicated no significant differences in attendance between the groups. Findings of negative educational or cognitive effects of health interventions are rare but not unprecedented [69] and suggest the need for experimental evaluations to test assumptions about the educational benefits of health programs. The finding of low overall achievement levels and minimal learning is consistent with the international literature, and findings from Kenya [36]. The causes are well documented and include: a lack of a culture of literacy, lack of effective teaching methods, poorly resourced teachers with large classes, poor health of children, and competition for children’s time at home [70,71].

Our study has a number of limitations. First, given the nature of the intervention, it was not possible to blind the parents, participants or field officers delivering the IST intervention to experimental assignment, which could have led to a possible “John Henry” effect whereby children in the control group adjust their behavior as they know they are not receiving the intervention, for example in risk aversion and treatment seeking behavior. Biomedical and educational assessors were blinded where feasible. Secondly, study children’s access to alternative malaria treatments outside of the school-based IST rounds was not monitored during the two years of the trial. However, due to the randomized design of the trial and the fact that the majority of infections in this age group and population were asymptomatic at assessment and screening points, we have no reason to suspect that study children’s access to treatment outside of this trial differed greatly across study groups. Finally, the lack of multiple testing adjustments may have increased the possibility of type 1 error, and results should be interpreted in light of this possible error, but it is unlikely to have masked a beneficial effect of IST.

Conclusion
In summary, our findings show there are no health or education benefits of implementing school-based IST with AL in a low to moderate transmission setting such as this study site, as a high proportion of children screened do not require treatment and those who do largely live in focal high transmission regions, where rapid re-infection occurs between screening rounds, and results in no lasting gains from treatment. Nevertheless, our results do highlight a potential role for schools as screening platforms. School screenings using RDTs could provide an operationally efficient method to initially identify transmission hotspots for targeted community control [72]. School surveys have proved a useful platform for defining heterogeneities in *Plasmodium* transmission over large geographical areas in a more rapid and low cost manner than community surveys [73,74]. The results from this study’s screening rounds present a case for the use of schools in also depicting local transmission heterogeneities, which can be extrapolated to the local community [75] and aid in developing targeted community-wide comprehensive interventions, such as localized indoor residual screening and larviciding, with biennial school screenings used to monitor the success of these interventions. The use of schools in this way is a focus of our current research.

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References

1. O’Meara WP, Mangeni JN, Steketee R, Greenwood B (2010) Changes in the burden of malaria in sub-Saharan Africa. Lancet Infect Dis 10: 545-555.

2. Ceesay SJ, Casals-Pascual C, Nwakanma DC, Walther M, Gomez-Escobar N, et al. (2010) Continued decline of malaria in The Gambia with implications for elimination. PLoS one 5: e12242.

3. Kalayjian BC, Malhotra I, Mungai PL, Holding PA, King CH (2013) Marked Decline in Malaria Prevalence among Pregnant Women and Their Offspring from 1996 to 2010 on the South Kenyan Coast. American Journal of Tropical Medicine and Hygiene.

4. Ceesay SJ, Casals-Pascual C, Erskine J, Anya SE, Duah NO, et al. (2008) Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. Lancet 372: 1545-1554.

5. O’Meara WP, Bejon P, Mwangi TW, Okiro EA, Peshu N, et al. (2008) Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet 372: 1555-1562.

6. Greenwood BM (2008) Control to elimination: implications for malaria research. Trends Parasitol 24: 449-454.

7. Smith DL, Guerra CA, Snow RW, Hay SI (2007) Standardizing estimates of the Plasmodium falciparum parasite rate. Malar J 6: 131.

8. Brooker S, Kolaczinski JH, Gitonga CW, Noor AM, Snow RW (2009) The use of schools for malaria surveillance and programme evaluation in Africa. Malaria J 8: 231.

9. Brooker S, Guyatt H, Omumbo J, Shretta R, Drake L, et al. (2000) Situation analysis of malaria in school-aged children in Kenya - what can be done? Parasitol Today 16: 183-186.

10. Japan International Cooperation Agency (JICA) (2012) Basic education sector analysis report: Kenya. Tokyo: JICA.

11. Kurtzhals JA, Addae MM, Akanmori BD, Dunyo S, Koram KA, et al. (1999) Anemia caused by asymptomatic Plasmodium falciparum infection in semi-immune African schoolchildren. Transactions of the Royal Society of Tropical Medicine and Hygiene 93: 623-627.

12. Menendez C, Fleming AF, Alonso PL (2000) Malaria-related anemia. Parasitology today (Personal ed) 16: 469-476.

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. Transactions of the Royal Society of Tropical Medicine and Hygiene 97: 161-165.

14. Kihara M, Carter JA, Newton CRJ (2006) The effect of Plasmodium falciparum on cognition: a systematic review. Tropical medicine & international health 11: 386-397.

15. Fernando SD, Rodrigo C, Rajapakse S (2010) The 'hidden' burden of malaria: cognitive impairment following infection. Malar J 9: 366.

16. Nankabirwa J, Wandera B, Kiwanuka N, Staedke SG, Kamya MR, et al. (2013) Asymptomatic Plasmodium Infection and Cognition among Primary Schoolchildren in a High Malaria Transmission Setting in Uganda. Am J Trop Med Hyg 10.4269/ajtmh.12-0633.

17. Al-Serour AIW, Grantham-McGregor SM, Greenwood B, Costello A (2000) Impact of asymptomatic malaria parasitaemia on cognitive function and school achievement of schoolchildren in the Yemen Republic. Parasitology 121 (Pt 4): 337-345.

18. Fernando D, de Silva D, Carter R, Mendis KN, Wickremasinghe R (2006) A randomized, double-blind, placebo-controlled, clinical trial of the impact of malaria prevention on the educational attainment of school children. Am J Trop Med Hyg 74: 386-393.

19. Moonen B, Cohen JM, Snow RW, Slutsker L, Drakeley C, et al. (2010) Operational strategies to achieve and maintain malaria elimination. Lancet 376: 1592-1603.

20. Bousema T, Griffin JT, Sauerwein RW, Smith DL, Churcher TS, et al. (2012) Hitting hotspots: spatial targeting of malaria for control and elimination. PLoS Med 9: e1001165.

21. Githeko AK, Brandling-Bennett AD, Beier M, Atieli F, Owaga M, et al. (1992) The reservoir of Plasmodium falciparum malaria in a holoendemic area of western Kenya. Trans R Soc Trop Med Hgy 86: 355-358.
22. Bousema JT, Gouagna LC, Drakeley CJ, Meutstege AM, Okech BA, et al. (2004) *Plasmodium falciparum* gametocyte carriage in asymptomatic children in western Kenya. Malar J 3: 18.
23. Brooker S (2009) Malaria Control in Schools: A toolkit on effective education sector responses to malaria in Africa. Washington D.C.: The World Bank
24. Clarke SE, Jukes MCH, Njagi JK, Khasakhala L, Cundill B, et al. (2008) Effect of intermittent preventive treatment of malaria on health and education in schoolchildren: a cluster-randomised, double-blind, placebo-controlled trial. Lancet 372: 127-138.
25. Barger B, Maiga H, Traore OB, Tekete M, Tombene I, et al. (2009) Intermittent preventive treatment using artemisinin-based combination therapy reduces malaria morbidity among school-aged children in Mali. Trop Med Int Health 14: 784-791.
26. Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, et al. (2010) Reducing *Plasmodium falciparum* malaria transmission in Africa: a model-based evaluation of intervention strategies. PLoS Med 7.
27. Kern SE, Tiono AB, Makanga M, Gbadoe AD, Premji Z, et al. (2011) Community screening and treatment of asymptomatic carriers of *Plasmodium falciparum* with artemether-lumefantrine to reduce malaria disease burden: a modelling and simulation analysis. Malar J 10: 210.
28. Tagbor H, Bruce J, Agbo M, Greenwood B, Chandramohan D (2010) Intermittent screening and treatment versus intermittent preventive treatment of malaria in pregnancy: a randomised controlled non-inferiority trial. PloS one 5: e14425.
29. Tiono AB, Ouedraogo A, Ogutu B, Diarra A, Coulibaly S, et al. (2013) A controlled, parallel, cluster-randomized trial of community-wide screening and treatment of asymptomatic carriers of *Plasmodium falciparum* in Burkina Faso. Malar J 12: 79.
30. Brooker S, Okello G, Njagi K, Dubeck MM, Halliday KE, et al. (2010) Improving educational achievement and anemia of school children: design of a cluster randomised trial of school-based malaria prevention and enhanced literacy instruction in Kenya. Trials 11.
31. Snow RW, Schellenberg JR, Peshu N, Forster D, Newton CR, et al. (1993) Periodicity and space-time clustering of severe childhood malaria on the coast of Kenya. Trans R Soc Trop Med Hyg 87: 386-390.
32. Mbogo CM, Mwangangi JM, Nzovu J, Gu W, Yan G, et al. (2003) Spatial and temporal heterogeneity of *Anopheles* mosquitoes and *Plasmodium falciparum* transmission along the Kenyan coast. The American journal of tropical medicine and hygiene 68: 734-742.
33. Mwangangi JM, Mbogo CM, Orindi BO, Muturi EJ, Midega JT, et al. (2013) Shifts in malaria vector species composition and transmission dynamics along the Kenyan coast over the past 20 years. Malaria J 12: 13.
34. Bustinduy AL, Thomas CL, Fiutem JJ, Parraga IM, Mungai PL, et al. (2011) Measuring fitness of Kenyan children with polyparasitic infections using the 20-meter shuttle run test as a morbidity metric. PLoS neglected tropical diseases 5: e1213.
35. Halliday KE, Karanja P, Turner EL, Okello G, Njagi K, et al. (2012) *Plasmodium falciparum*, anemia and cognitive and educational performance among school children in an area of moderate malaria transmission: baseline results of a cluster randomized trial on the coast of Kenya. Trop Med Int Health 17: 532-549.
36. Dubeck MM, Jukes MCH, Okello G (2012) Early primary literacy instruction in Kenya. Comparative Education Review 56: 48-68.
37. Martinez EZ, Louzada-Neto F, Derchain SFM, Achcar JA, Gontijo RC, et al. (2008) Bayesian estimation of performance measures of cervical cancer screening tests in the presence of covariates and absence of a gold standard. Cancer Inform 6: 33-46.
38. Division of Malaria Control Ministry of Public Health and Sanitation (2009) National Malaria Strategy 2009-2017. Nairobi: Kenya NMCP.
39. Manly T, Robertson IH, Anderson V, Nimmo-Smith I (1999) Test of everyday attention for children: TEA-Ch; Bury St Edmunds, UK: Thames Valley Test Company.
40. Luria AR (1966) Higher Cortical Functions in Man. New York: Basic Books.
41. Invernizzi M, Sullivan A, Meier J, Swank L (2004) PALS: Phonological awareness literacy screening. Charlottesville, VA: University of Virginia.
42. Benoist B, McLean E, Egli I, Cogswell M (2008) Worldwide prevalence of anemia 1993-2003: WHO global database on anemia. WHO.

43. Filmer D, Pritchett LH (2001) Estimating wealth effects without expenditure data--or tears: an application to educational enrollments in states of India. Demography 38: 115-132.

44. WHO (2007) Anthroplus: Growth Reference 5-19 years In: WHO, editor.

45. Hayes R, J., Moulton L, H. (2009) Cluster Randomised Trials Hall C, editor. UK: crc pRESS.

46. Bundy D (2011) Rethinking School Health: A key component of education for all. Washington: World Bank.

47. Okello G, Jones C, Bonareri M, Ndegwa SN, Mcharo C, et al. (2013) Challenges for consent and community engagement in the conduct of cluster randomized trial among school children in low income settings: experiences from Kenya. Trials 14: 142.

48. Bejon P, Warimwe G, Mackintosh CL, Mackinnon MJ, Kinyanjui SM, et al. (2009) Analysis of immunity to febrile malaria in children that distinguishes immunity from lack of exposure. Infect Immun 77: 1917-1923.

49. Bousema T, Kreuels B, Gosling R (2011) Adjusting for heterogeneity of malaria transmission in longitudinal studies. I Infect Dis 204: 1-3.

50. Sowunmi A, Gbotsoso GO, Happi CT, Adedeji AA, Fehintola FA, et al. (2007) Therapeutic efficacy and effects of artemether-lumefantrine and amodiaquine-sulfalene-pyrimethamine on gametocyte carriage in children with uncomplicated Plasmodium falciparum malaria in southwestern Nigeria. Am J Trop Med Hyg 77: 235-241.

51. Woodring JV, Ogutu B, Schnabel D, Waitumbi JN, Olsen CH, et al. (2010) Evaluation of recurrent parasitemia after artemether-lumefantrine treatment for uncomplicated malaria in children in western Kenya. Am J Trop Med Hyg 83: 458-464.

52. Nambozi M, Van Geertruyden J-P, Hachizovu S, Chaponda M, Mukwamataba D, et al. (2011) Safety and efficacy of dihydroartemisinin-piperaquine versus artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Zambian children. Malaria J 10: 50.

53. Ochola LB, Vounatsou P, Smith T, Mabaso MLH, Newton CRJC (2006) The reliability of diagnostic techniques in the diagnosis and management of malaria in the absence of a gold standard. Lancet Infect Dis 6: 582-588.

54. Speybroeck N, Praet N, Claes F, Van Hong N, Torres K, et al. (2011) True versus apparent malaria infection prevalence: the contribution of a Bayesian approach. PloS one 6: e16705.

55. Gonçalves L, Subtil A, de Oliveira MR, do Rosário V, Lee P-W, et al. (2012) Bayesian latent class models in malaria diagnosis. PloS one 7: e40633.

56. Okell LC, Ghani AC, Lyons E, Drakeley CJ (2009) Submicroscopic infection in Plasmodium falciparum-endemic populations: a systematic review and meta-analysis. J Infect Dis 200: 1509-1517.

57. Okell LC, Bousema T, Griffin JP, Ouédraogo AL, Ghani AC, et al. (2012) Factors determining the occurrence of submicroscopic malaria infections and their relevance for control. Nature communications 3: 1237.

58. Dinko B, Oguike MC, Larbi JA, Bousema JT, Sutherland CJ (2013) Persistent detection of Plasmodium falciparum, P. malariae, P. ovale curtisi and P. ovale wallikeri after ACT treatment of asymptomatic Ghanaian school-children. International Journal for Parasitology: Drugs and Drug Resistance 3: 45-50.

59. Ochola LB, Vounatsou P, Smith T, Mabaso MLH, Newton CRJC (2006) The reliability of diagnostic techniques in the diagnosis and management of malaria in the absence of a gold standard. Lancet Infect Dis 6: 582-588.

60. Okello G, Ndegwa SN, Halliday KE, Hanson K, Brooker SJ, et al. (2012) Local perceptions of intermittent screening and treatment for malaria in school children on the south coast of Kenya. Malaria J 11: 185.

61. Drake TL, Okello G, Njagi K, Halliday KE, Jukes MC, et al. (2011) Cost analysis of school-based intermittent screening and treatment of malaria in Kenya. Malaria J 10: 273.
62. Piola P, Fogg C, Bajunirwe F, Biraro S, Grandesso F, et al. (2005) Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated *Plasmodium falciparum* malaria in Mbarara, Uganda: a randomised trial. Lancet 365: 1467-1473.

63. Borrmann S, Sasi P, Mwai L, Bashraheel M, Abdallah A, et al. (2011) Declining responsiveness of *Plasmodium falciparum* infections to artemisinin-based combination treatments on the Kenyan coast. PloS one 6: e26005.

64. Agarwal A, McMorrow M, Onyango P, Otieno K, Odero C, et al. (2013) A randomized trial of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated malaria among children in western Kenya. Malaria J 12: 254.

65. National Coordination Agency for Population and Development (2005) Kwale District Strategic Plan 2005-2010 for implementation of the National Population Policy for Sustainable Development. Nairobi: National Coordination Agency for Population and Development. 1-55p

66. Kenya Food Security Steering Group (2012) The 2011/12 Short Rains Season Assessment Report. Nairobi: Kenya Food Security Steering Group. 1-42 p.

67. Pullan RL, Gitonga C, Mwandawiro C, Snow RW, Brooker SJ (2013) Estimating the relative contribution of parasitic infections and nutrition for anemia among school-aged children in Kenya: a subnational geostatistical analysis. BMJ Open 3.

68. Smith LA, Jones C, Adjei RO, Antwi GD, Afrah NA, et al. (2010) Intermittent screening and treatment versus intermittent preventive treatment of malaria in pregnancy: user acceptability. Malar J 9: 18.

69. Hamadani JD, Fuchs GJ, Osendarp SJ, Khatun F, Huda SN, et al. (2001) Randomized controlled trial of the effect of zinc supplementation on the mental development of Bangladeshi infants. The American journal of clinical nutrition 74: 381-386.

70. Heyneman SP, Loxley WA (1983) The effect of primary-school quality on academic achievement across twenty-nine high- and low-income countries. Ajs 88: 1162-1194.

71. Bhargava A, Jukes M, Ngorosho D, Khilma C, Bundy DA (2005) Modeling the effects of health status and the educational infrastructure on the cognitive development of Tanzanian schoolchildren. American journal of human biology : the official journal of the Human Biology Council 17: 280-292.

72. Takem EN, Affara M, Amambua-Ngwa A, Okebe J, Ceesay SJ, et al. (2013) Detecting Foci of Malaria Transmission with School Surveys: A Pilot Study in the Gambia. PloS one 8.

73. Gitonga CW, Karanja PN, Kihara J, Mwanje M, Juma E, et al. (2010) Implementing school malaria surveys in Kenya: towards a national surveillance system. Malaria J 9: 306.

74. Ashton RA, Kefyalew T, Tesfaye G, Pullan RL, Yadeta D, et al. (2011) School-based surveys of malaria in Oromia Regional State, Ethiopia: a rapid survey method for malaria in low transmission settings. Malaria J 10: 25.

75. Stevenson J, Stresman G, Gitonga CW, Gillig J, Owaga C, et al. (2013) Reliability of school surveys in estimating geographic variation in malaria transmission in the Western Kenyan highlands. PloS one 8.

Tables and figures
### Table 1. Baseline characteristics of 5233 study children in the 50 control and 51 IST intervention schools.

| Characteristics; n (%) | Control | Intervention |
|-------------------------|---------|--------------|
| **School characteristics** b | | |
| Exam score | Mean (sd) | 223.4 (27.7) | 225.8 (29.0) |
| School size | Median (IQR) [min, max] | 505 (308, 961) [85,4891] | 568 (389, 692) [225,1344] |
| Enrolled class 1 | Mean (sd) [min, max] | 24.4 (3.3) [10, 30] | 25.8 (1.5) [23, 30] |
| Enrolled class 5 | Mean (sd) [min, max] | 26.0 (4.6) [8, 30] | 27.3 (3.3) [16, 32] |
| School programs | | | |
| Feeding | 22 (44.0) | 27 (52.9) |
| De-worming | 50 (100.0) | 49 (96.1) |
| Malaria control | 9 (18.4) | 12 (23.5) |
| **Child characteristics** b | | |
| Age c | Mean (sd) | 10.1 (2.8) | 10.3 (2.8) |
| 5-9 | 1041 (41.2) | 1069 (39.5) |
| 10-12 | 877 (34.8) | 925 (34.1) |
| 13-20 | 605 (24.0) | 716 (26.4) |
| Sex | | | |
| Male | 1257 (49.8) | 1319 (48.7) |
| Child sleeps under net | | | |
| Usually | 1668 (67.3) | 1682 (63.1) |
| Treated net d | 1357 (83.3) | 1308 (80.5) |
| Last night b | 1606 (96.3) | 1609 (95.7) |
| Nutritional Status | | | |
| Underweight | 266 (27.0) | 231 (23.9) |
| Stunted | 600 (25.2) | 612 (24.9) |
| Thin | 482 (20.2) | 450 (18.3) |
| **Household characteristics** b | | |
| Parental Education | | | |
| No schooling | 726 (29.4) | 925 (34.7) |
| Primary schooling | 1292 (52.2) | 1381 (51.8) |
| Secondary schooling | 353 (14.3) | 278 (10.4) |
| Higher education | 102 (4.1) | 83 (3.1) |
| Socioeconomic status | | | |
| Poorest | 440 (17.7) | 655 (24.4) |
| Poor | 483 (19.5) | 564 (21.0) |
| Median | 465 (18.7) | 495 (18.5) |
| Less poor | 524 (21.1) | 509 (19.0) |
| Least poor | 572 (23.0) | 458 (17.1) |
| Household size | | | |
| 1-5 | 697 (28.1) | 703 (26.4) |
| 6-9 | 1444 (58.3) | 1580 (59.3) |
| 10-31 | 338 (13.6) | 382 (14.3) |
| **Study endpoints-baseline** e | | |
| Anemia prevalence f (k=0.21) | Age-sex specific | 1073 (45.2) | 1114 (45.5) |
| Severe (<70g/L) | 14 (0.6) | 14 (0.6) |
| Moderate (70-89 g/L) | 43 (1.8) | 55 (2.2) |
| Mild (90-109 g/L) | 530 (22.3) | 518 (21.1) |
| None (≥110 g/L) | 1786 (75.3) | 1864 (76.1) |
| Hemoglobin (g/L) | Mean (sd) | 117.3 (13.0) | 117.5 (13.7) |
**Table 2: Summary information for 2710 study children in the IST intervention group by screening round.**

| IST Round | Season | Study children a | N (%) Screened | N (%) RDT Positive | N (%) Treated | N (%) Supervised treatment b | RDT sensitivity /specificity c |
|-----------|--------|------------------|----------------|-------------------|--------------|----------------------------|-----------------------------|
| Feb-Mar 2010 | Dry    | 2674 (98.7)      | 2454 (91.8)    | 453 (18.5)        | 449 (99.1)   | 435 (96.9)                 | 78.5 / 90.6                |
| Jun-Jul 2010 | Wet    | 2654 (97.9)      | 2430 (91.6)    | 466 (19.2)        | 465 (99.8)   | 440 (94.6)                 | 89.2 / 90.4                |
| Sept 2010    | Wet    | 2651 (97.8)      | 2368 (89.3)    | 444 (18.8)        | 443 (99.8)   | 422 (95.3)                 | 94.6 / 90.3                |
| Feb-Mar 2011 | Dry    | 2631 (97.1)      | 2291 (87.1)    | 340 (14.8)        | 335 (98.5)   | 306 (91.3)                 | 68.7 / 91.9                |
| Oct 2011     | Wet    | 2621 (96.7)      | 2157 (82.3)    | 345 (16.0)        | 338 (98.0)   | 276 (81.7)                 | NA                         |
| TOTALS       |        | 13231            | 11700 (88.4)   | 2048 (17.5)       | 2030 (99.1)  | 1879 (92.6)                | 82.7 / 90.8                |

sensitivity and specificity of RDTs compared to expert microscopy is displayed

a Study children are shown as a percentage of the 2710 initially eligible for the intervention and loss at each stage represents withdrawals and/or deaths. Child transfer events are not included.

b Children treated who were directly observed taking doses 1,3 and 5 in school at the correct time and who reported taking the evening doses.

c Microscopy results not available for visit 5
Table 3. Effect of the IST intervention at 12 and 24 months follow-up on health outcomes anemia and *Plasmodium falciparum* prevalence for study children.

| Outcome                        | Control (50 schools) | Intervention (51 schools) | Risk ratio* (95% CI) | p-value | Cluster-size; range (average) |
|-------------------------------|----------------------|---------------------------|----------------------|---------|-----------------------------|
|                               | n (%)b               | n (%)b                    |                      |         |                             |
| 12 month follow-up            | N=2478               | N=2631                    |                      |         |                             |
| Prevalence of anemia*         |                      |                           |                      |         |                             |
| Unadjusted                    | 2146                 | 837 (39.0%)               | 2297                 | 920 (40.1%) | 1.03 (0.91,1.16) | 0.646 | 15-55 (44.0) |
| Adjusted                      | 2048                 | 788 (38.5%)               | 2142                 | 858 (40.1%) | 1.03 (0.93,1.13) | 0.621 | 15-55 (41.5) |
| Prevalence of *P. falciparum* |                      |                           |                      |         |                             |
| Unadjusted                    | 2106                 | 302 (14.3%)               | 2276                 | 243 (10.7%) | 0.76 (0.49,1.18) | 0.221 | 11-55 (43.4) |
| Adjusted                      | 2106                 | 302 (14.3%)               | 2276                 | 243 (10.7%) | 0.71 (0.46,1.11) | 0.131 | 11-55 (43.4) |
| 24 months follow-up           | N=2468               | N=2619                    |                      |         |                             |
| Prevalence of anemia*         |                      |                           |                      |         |                             |
| Unadjusted                    | 2027                 | 809 (39.9%)               | 2173                 | 910 (41.9%) | 1.05 (0.91,1.21) | 0.514 | 15-55 (41.6) |
| Adjusted                      | 1935                 | 765 (39.5%)               | 2027                 | 842 (41.5%) | 1.00 (0.90,1.11) | 0.953 | 14-55 (39.5) |
| Prevalence of *P. falciparum* |                      |                           |                      |         |                             |
| Unadjusted                    | 2001                 | 169 (8.5%)                | 2139                 | 253 (11.8%) | 1.42 (0.84,2.42) | 0.192 | 15-55 (41.0) |
| Adjusted                      | 2001                 | 169 (8.5%)                | 2139                 | 253 (11.8%) | 1.53 (0.89,2.62) | 0.124 | 15-55 (41.0) |

Results presented (i) for all children with outcome data (unadjusted) and (ii) for those with baseline measurements of each outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis. N=number of children eligible for follow up (not withdrawn or deceased)

* Risk ratios (intervention/control) presented for binary outcomes (anemia & *P. falciparum* prevalence) and are obtained from GEE analysis accounting for school-level clustering.

Number and percentage with outcome

Age-sex specific anemia was defined using age and sex corrected WHO thresholds of hemoglobin concentration: <110g/l in children under 5 years; <115g/l in children 5 to 11 years; <120g/l in females 12 years and over and males 12 to 14.99 years old; and <130g/l in males ≥ 15 years. All female adolescents are assumed to not be pregnant.

Not including baseline *P. falciparum* infection

Unadjusted: All children with outcome measures, not adjusted for any baseline or study design characteristics.

Adjusted: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available.
Table 4. Effect of the IST intervention at 9 and 24 months follow-up on sustained attention outcomes for younger (class 1) and older (class 5) children.

| Outcome                          | Control (50 schools) | Intervention (51 schools) | Mean difference\(^{a}\) (95% CI) | p-value \(\times 10^{3}\) | Cluster-size; range (mean) |
|----------------------------------|----------------------|---------------------------|----------------------------------|---------------------------|---------------------------|
| **9 months follow-up**           |                      |                           |                                  |                           |                           |
| CLASS 1 (median age:8, range: 5-15) | N=1210               | N=1281                    |                                  |                           |                           |
| Sustained Attention \(^{c}\) (score:0-20) |                      |                           |                                  |                           |                           |
| Unadjusted                       | 1070                 | 1162                      | 8.43 (3.76)                      | -0.04 (-0.58,0.51)        | 0.895                      |
| Adjusted                         | 1030                 | 1144                      | 8.43 (3.77)                      | -0.13 (-0.66,0.39)        | 0.623                      |
| CLASS 5 (median age:12, range: 8-18) | N=1283               | N=1365                    |                                  |                           |                           |
| Sustained Attention \(^{d}\) (score:0-20) |                      |                           |                                  |                           |                           |
| Unadjusted                       | 1180                 | 1231                      | 13.35 (5.13)                     | -0.09 (-0.77,0.56)        | 0.799                      |
| Adjusted                         | 1178                 | 1221                      | 13.40 (5.10)                     | -0.21 (-0.81,0.39)        | 0.490                      |
| **24 months follow-up**          |                      |                           |                                  |                           |                           |
| CLASS 1 (median age:8, range: 5-15) | N=1201               | N=1269                    |                                  |                           |                           |
| Sustained Attention \(^{c}\) (score:0-20) |                      |                           |                                  |                           |                           |
| Unadjusted                       | 960                  | 1059                      | 13.20 (4.96)                     | -0.26 (-0.95,0.43)        | 0.456                      |
| Adjusted                         | 923                  | 1041                      | 13.18 (4.96)                     | -0.44 (-1.09,0.21)        | 0.180                      |
| CLASS 5 (median age:12, range: 9-18) | N=1267               | N=1350                    |                                  |                           |                           |
| Sustained Attention \(^{d}\) (score:0-20) |                      |                           |                                  |                           |                           |
| Unadjusted                       | 1007                 | 1052                      | 14.66 (4.60)                     | 0.40 (-0.14,0.94)         | 0.144                      |
| Adjusted                         | 1006                 | 1044                      | 14.70 (4.58)                     | 0.28 (-0.23,0.79)         | 0.283                      |

Results presented (i) for all children with outcome data (unadjusted) and (ii) for those with baseline measurements of each outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis.

N=number of children eligible for follow up (not withdrawn or deceased)

\(^{a}\) Mean difference (intervention-control) are obtained from GEE analysis accounting for school-level clustering.

\(^{b}\) Mean score and sd at follow-up

\(^{c}\) Pencil tap test was conducted at baseline and single digit code transmission task was conducted at 9 and 24 months follow-ups.

\(^{d}\) Double digit code transmission was conducted at baseline and both follow-ups.

**Unadjusted**: All children with outcome measures, not adjusted for any baseline or study design characteristics.

**Adjusted**: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available.
Table 5. Effect of the IST intervention at 9 and 24 months follow-up on educational achievement (spelling and arithmetic) outcomes for younger (class 1) and older (class 5) children.

| Outcome; N (%) | Control (50 schools) | Intervention (51 schools) | Mean difference a (95% CI) | p-value | Cluster-size; range (mean) |
|---------------|----------------------|---------------------------|---------------------------|---------|---------------------------|
| **9 months follow-up** |                       |                           |                           |         |                           |
| CLASS 1 (median age: 8, range: 5-15) |                       |                           |                           |         |                           |
| Spelling (score: 0-20) e |                       |                           |                           |         |                           |
| Unadjusted     | 1068                 | 11.70 (4.59)              | 1162                     | 10.47 (4.57) | -1.23 (-2.21,-0.24) | 0.015 | 8-27 (22.1) |
| Adjusted       | 1060                 | 11.69 (4.59)              | 1133                     | 10.49 (4.58) | -0.67 (-1.26,-0.08) | 0.026 | 8-27 (21.7) |
| Arithmetic (score: 0-30) f |                       |                           |                           |         |                           |
| Unadjusted     | 1071                 | 4.21 (3.13)               | 1162                     | 4.04 (3.26) | -0.17 (-0.60, 0.26) | 0.433 | 8-27 (22.1) |
| Adjusted       | 1069                 | 4.21 (3.12)               | 1143                     | 4.07 (3.28) | -0.21 (-0.54, 0.12) | 0.214 | 8-27 (21.9) |
| CLASS 5 (median age: 12, range: 8-18) |                       |                           |                           |         |                           |
| Spelling (score: 0-75) |                       |                           |                           |         |                           |
| Unadjusted     | 1169                 | 31.34 (12.61)             | 1223                     | 28.73 (12.36) | -2.73 (-5.26,-0.19) | 0.035 | 8-30 (23.7) |
| Adjusted       | 1154                 | 31.37 (12.60)             | 1214                     | 28.76 (12.34) | -0.31 (-1.26,0.63) | 0.515 | 8-30 (23.4) |
| Arithmetic (score: 0-30) |                       |                           |                           |         |                           |
| Unadjusted     | 1180                 | 31.15 (5.49)              | 1229                     | 30.72 (5.17) | -0.49 (-1.40, 0.42) | 0.294 | 8-30 (23.9) |
| Adjusted       | 1173                 | 31.14 (5.50)              | 1210                     | 30.73 (5.17) | 0.13 (-0.41, 0.68) | 0.629 | 8-30 (23.6) |
| **24 months follow-up** |                       |                           |                           |         |                           |
| CLASS 1 (median age: 8, range: 5-15) |                       |                           |                           |         |                           |
| Spelling (score: 0-20) e |                       |                           |                           |         |                           |
| Unadjusted     | 961                  | 12.03 (3.05)              | 1062                     | 11.04 (3.49) | -0.97 (-1.54,-0.40) | 0.001 | 8-26 (20.0) |
| Adjusted       | 954                  | 12.02 (3.05)              | 1036                     | 11.04 (3.50) | -0.65 (-1.11,-0.20) | 0.005 | 8-25 (19.7) |
| Arithmetic (score: 0-30) |                       |                           |                           |         |                           |
| Unadjusted     | 962                  | 5.97 (3.05)               | 1061                     | 5.38 (2.97) | -0.59 (-1.08,-0.10) | 0.018 | 8-26 (20.0) |
| Adjusted       | 960                  | 5.97 (3.04)               | 1042                     | 5.40 (2.97) | -0.60 (-1.02,-0.19) | 0.005 | 8-25 (19.9) |
| CLASS 5 (median age: 12, range: 9-18) |                       |                           |                           |         |                           |

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### Spelling (score: 0-78)*

|                  | Unadjusted | Adjusted |
|------------------|------------|----------|
|                  |            |          |
|                  | 1010       | 996      |
| Mean difference  | 35.28 (12.91) | 35.33 (12.85) |
| (intervention-control) | 33.97 (12.79) | 34.04 (12.75) |
|                  | -1.58 (-4.01, 0.85) | 0.71 (-0.34, 1.76) |
|                  | 0.202      | 0.183    |
|                  | 6-31 (20.5) | 6-29 (20.3) |

### Arithmetic(score:0-30)†

|                  | Unadjusted | Adjusted |
|------------------|------------|----------|
|                  |            |          |
|                  | 1016       | 1009     |
| Mean difference  | 21.20 (5.47) | 21.20 (5.48) |
| (intervention-control) | 20.15 (5.68) | 20.18 (5.69) |
|                  | -1.07 (-2.15, -0.00) | -0.49 (-1.32, 0.34) |
|                  | 0.050      | 0.243    |
|                  | 6-31 (20.6) | 6-29 (20.3) |

Results presented (i) for all children with outcome data (unadjusted) and (ii) for those with baseline measurements of each outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis.

N=number of children eligible for follow up (not withdrawn or deceased)

* Mean difference (intervention-control) for scores on spelling and arithmetic are obtained from GEE analysis accounting for school-level clustering

† Mean score and sd at follow

The same class 1 spelling task was given at baseline, 9 and 24 months follow-ups, with different words used for the 24 month follow-up.

Same addition task conducted at 9 months follow-up and at baseline, hence baseline adjustment is for the same task.

The same class 5 spelling task was given at baseline, 9 and 24 months follow-ups, with different words used for the 24 month follow-up.

Same arithmetic task conducted at baseline, 9 and 24 months follow-ups, with different sums used for the 24 month follow-up.

Addition task conducted at baseline and arithmetic task containing addition, subtraction, multiplication and division conducted at 24 months follow-up, hence baseline adjustment for different task.

**Unadjusted**: All children with outcome measures, not adjusted for any baseline or study design characteristics.

**Adjusted**: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available.
Figure 1

Map of the study area and schools. Schools assigned to the IST intervention are shown in blue and schools assigned to the control group are shown in yellow. Insert shows the location of the study site in Kenya.
Figure 2
Study design diagram. This figure depicts the randomization procedures.
Figure 3

**Trial profile.** The flow of children and clusters in the 50 control 51 IST intervention groups at all assessment points throughout the two year study period. FU1 indicates follow-up 1 and FU2 indicates follow-up 2. Cluster size is presented as mean (SD) [min, max].
Supporting Information

Text S1
Methods for the missing data models

Table S1
Baseline measures for 5233 study children with missing 12 months follow-up health data vs. those not missing 12 months follow-up health data across both the control and IST intervention groups.

Table S2
Baseline measures for 5233 study children with missing 24 months follow-up health data vs. those not missing 24 months follow-up health data across both the control and IST intervention groups.

Table S3
Results from missing data analysis for anemia. Effect of the IST intervention at 12 and 24 months follow-up on the primary health outcome of anemia for study children combined using a longitudinal, random effects regression modeling approach. Results presented (i) for all children with either 12 or 24 months follow-up measurements of the outcome (unadjusted), (ii) for those with baseline measurements of the outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis, and (iii) for those additionally with baseline measures of parental education, SES and baseline educational level (measured by baseline spelling) as further predictors of missingness.

Table S4
Baseline measures for study children with missing 9 months follow-up education data vs. those not missing 9 months follow-up education data across both the control and intervention groups.

Table S5
Baseline measures for study children with missing 24 months follow-up education data vs. those not missing 24 months follow-up education data across both the control and intervention groups.

Table S6
Results from missing data analysis for sustained attention. Effect of the IST intervention at 9 and 24 months follow-up on sustained attention outcomes for younger (class 1) and older (class 5) children combined using a longitudinal, random effects regression modeling approach. Results presented (i) for all children with either 9 or 24 months follow-up measurements of the outcome (unadjusted), (ii) for those with baseline measurements of the outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis, and (iii) for those additionally with baseline measures of parental education, SES and baseline educational level (measured by baseline spelling) as further predictors of missingness.

Table S7
Results from missing data analysis for spelling. Effect of the IST intervention at 9 and 24 months follow-up on spelling outcomes for younger (class 1) and older (class 5) children combined using a longitudinal, random effects regression modeling approach. Results presented (i) for all children with either 9 or 24 months follow-up measurements of the outcome (unadjusted), (ii) for those with baseline measurements of the outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis, and (iii) for those additionally with baseline measures of parental education, SES and baseline educational level (measured by baseline spelling) as further predictors of missingness.

Table S8
Sensitivity analyses considering transfers across the study period. Effect of the IST intervention at 12 and 24 months follow-up on health outcomes for study children. Results presented (i) for all children with either 12 or 24 months follow-up measurements of the outcome (unadjusted) with children who transferred schools excluded and (ii) for those with baseline measurements of each outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis with children who transferred schools excluded.
Table S9
Analysis stratified by categories of *P.falciparum* prevalence at baseline. Effect of the IST intervention at 12 and 24 months follow-up on the prevalence of anemia, by baseline prevalence category of *P.falciparum* (control school prevalence estimated using 12 month follow-up data) with adjustment for age, sex and stratification effects.

Table S10
Analysis stratified by number of AL treatments received. Effect of the IST intervention at 12 and 24 months follow-up within the IST intervention group by number of positive results and subsequent treatments received at the individual level.

Checklist S1
CONSORT checklist

Protocol S1
Study Protocol
Methods for the missing data models

We performed a missing data analysis for the primary outcomes of age-specific anemia and sustained attention and for the secondary outcome of spelling, for which we identified a negative effect of the IST intervention in Class 1 children. In order to gain power and account for missing data, we used a likelihood-based approach and fitted random effects models to the one-year and two-year follow-up data simultaneously. We included the following variables in all models: age, sex, literacy group, school-mean exam score and a baseline measure, where possible. The logit link was used for binary outcomes to obtain odds ratios of the intervention effect. As a consequence, the intervention effects from these models are not directly comparable to the population-averaged risk ratios obtained from the GEE model. As a consequence, we also present results from the unadjusted models for comparison to the models additionally adjusted for predictors of missingness. Time was modeled as a categorical variable in all models so that we did not assume a specific linear effect of time. Specifically, we allowed the IST effect to differ at the two time-points by including an interaction between IST and time. We additionally adjusted for variables seen to predict missingness. See Tables S1 and S2 for predictors of missingness for health outcomes at follow-up 1 and follow-up 2 respectively, in both the control and intervention groups. Tables S3 and S4 show the equivalent data for educational outcomes at follow-up 1 and follow-up 2 respectively. Specifically we adjusted for SES, parental education and baseline educational level as measured by baseline spelling score (standardized by subtracting year-group baseline mean and scaled by year-group SD) in both the health and educational outcome analyses. By accounting for predictors of missingness in the models, we can obtain valid estimates of the intervention effect in the presence of missing follow-up data. Furthermore, we gain power by simultaneously modeling the follow up 1 and follow-up 2 data. For results of missingness analyses for health and education outcomes please see Tables S5 and S6.
Table S1. Baseline measures for 5233 study children with missing 12 months follow-up health data vs. those not missing 12 months follow-up health data across both the control and IST intervention groups.

| Characteristic; n (%) | CONTROL GROUP | INTERVENTION GROUP |
|-----------------------|---------------|--------------------|
|                       | Missing outcome data | Outcome data available | Missing outcome data | Outcome data available |
| Child characteristics  | N=375 | N=2148 | N=412 | N=2298 |
| Age                   |               |                   |                   |                   |
| Mean (sd)             | 10.4 (3.1)    | 10.1 (2.8)        | 10.6 (3.1)        | 10.3 (2.8)        |
| 5-9                   | 155 (41.3)    | 886 (41.2)        | 155 (37.6)        | 914 (39.8)        |
| 10-12                 | 107 (28.5)    | 770 (35.9)        | 120 (29.1)        | 805 (35.0)        |
| 13-20                 | 113 (30.1)    | 492 (22.9)        | 137 (33.3)        | 579 (25.2)        |
| Sex                   |               |                   |                   |                   |
| Male                  | 193 (51.5)    | 1064 (49.5)       | 208 (50.5)        | 1111 (48.3)       |
| Child sleeps under net|               |                   |                   |                   |
| Usually               | 229 (63.6)    | 1439 (67.9)       | 238 (60.1)        | 1444 (63.7)       |
| Last night            | 223 (97.4)    | 1383 (96.1)       | 225 (94.5)        | 1384 (95.8)       |
| Nutritional Status    |               |                   |                   |                   |
| Underweight           | 42 (30.7)     | 224 (26.4)        | 26 (22.6)         | 205 (24.1)        |
| Stunted               | 80 (24.1)     | 520 (25.3)        | 72 (22.4)         | 540 (25.2)        |
| Thin                  | 64 (19.3)     | 418 (20.4)        | 47 (14.6)         | 403 (18.8)        |
| Household characteristics|             |                   |                   |                   |
| Parental Education    |               |                   |                   |                   |
| No schooling          | 101 (28.2)    | 625 (29.6)        | 158 (39.6)        | 767 (33.8)        |
| Primary schooling     | 180 (50.3)    | 1112 (52.6)       | 196 (49.1)        | 1185 (52.2)       |
| Secondary schooling   | 59 (16.5)     | 294 (13.9)        | 30 (7.5)          | 248 (10.9)        |
| Higher education      | 18 (5.0)      | 84 (4.0)          | 15 (3.8)          | 68 (3.0)          |
| Socioeconomic status  |               |                   |                   |                   |
| Poorest               | 67 (18.6)     | 373 (17.6)        | 98 (24.5)         | 557 (24.4)        |
| Poor                  | 84 (23.3)     | 399 (18.8)        | 88 (22.0)         | 476 (20.9)        |
| Median                | 63 (17.5)     | 402 (18.9)        | 84 (21.0)         | 411 (18.0)        |
| Less poor             | 60 (16.7)     | 464 (21.8)        | 72 (18.0)         | 437 (19.2)        |
| Least poor            | 86 (23.9)     | 486 (22.9)        | 58 (14.5)         | 400 (17.5)        |
| Household size        |               |                   |                   |                   |
| 1-5                   | 122 (33.9)    | 575 (27.1)        | 117 (29.5)        | 586 (25.8)        |
| 6-9                   | 193 (53.6)    | 1251 (59.0)       | 211 (53.3)        | 1369 (60.3)       |
| 10-31                 | 45 (12.5)     | 293 (13.8)        | 68 (17.2)         | 314 (13.8)        |
| Study endpoints-baseline | Class 1 N=183 | Class 1 N=1039 | Class 1 N=191 | Class 1 N=1126 |
|                        | Class 5 N=192 | Class 5 N=1109 | Class 5 N=221  | Class 5 N=1172  |
| Anemia prevalence     |               |                   |                   |                   |
| Age-sex specific      | 144 (44.4)    | 929 (45.3)        | 128 (41.6)        | 986 (46.0)        |
### Table S2. Baseline measures for 5233 study children with missing 24 months follow-up health data vs. those not missing 24 months follow-up health data across both the control and IST intervention groups.

| Characteristic; n (%) | CONTROL GROUP | INTERVENTION GROUP |
|-----------------------|---------------|--------------------|
|                       | Missing outcome data | Outcome data available | Missing outcome data | Outcome data available |
| Child characteristics  | N=496 | N=2027 | N=536 | N=2174 |
| **Age**               |          |          |          |          |
| Mean (sd)             | 10.5 (3.1) | 10.0 (2.8) | 10.9 (3.1) | 10.2 (2.7) |
| 5-9                   | 196 (39.5) | 845 (41.7) | 184 (34.3) | 885 (40.7) |

* % of non-missing children in each study group presented for categorized data. For continuous data mean(sd) [min,max] is presented; 

* Not measured at baseline in the control group; 

* Presented as mean(sd) [min,max] 

* In class 1 sustained attention was measured by the “pencil tap test” and in class 5 sustained attention was measured by the “two digit code transmission test”.

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| Severe (<70g/L) | 2 (0.6) | 12 (0.6) | 0 (0.0) | 14 (0.7) |
|-----------------|---------|----------|---------|---------|
| Moderate (70-89 g/L) | 10 (3.1) | 33 (1.6) | 7 (2.3) | 48 (2.2) |
| Mild (90-109 g/L) | 66 (20.4) | 464 (22.6) | 55 (17.9) | 463 (21.6) |
| None (≥110 g/L) | 246 (75.9) | 1540 (75.2) | 246 (79.9) | 1618 (75.5) |

**Hemoglobin (g/L)**

|          | Mean (sd) |          | Mean (sd) |          |
|----------|-----------|----------|-----------|----------|
| Severe   | 117.7 (13.6) | 117.3 (12.9) | 118.9 (13.3) | 117.3 (13.7) |
| Moderate | -         |          | 26 (8.6) | 285 (13.6) |
| Mild     | 66 (20.4) | 464 (22.6) | 55 (17.9) | 463 (21.6) |
| None     | 246 (75.9) | 1540 (75.2) | 246 (79.9) | 1618 (75.5) |

**P.falciparum prevalence**

|          |          |          |          |          |
|----------|----------|----------|----------|----------|
| Class 1  | 11.9 (6.7) [0, 20] | 11.9 (6.7) [0, 20] | 11.8 (6.6) [0, 20] | 12.2 (6.6) [0, 20] |
| Class 5  | 9.9 (6.1) [0, 20] | 9.9 (6.0) [0, 20] | 9.6 (5.7) [0, 20] | 10.6 (5.7) [0, 20] |
|          | 24.0 (11.6) [0, 51] | 28.6 (11.7) [0, 63] | 24.2 (11.1) [0, 56] | 26.1 (11.2) [0, 59] |
|          | 28.6 (6.1) [5, 38] | 29.5 (5.5) [0, 38] | 27.2 (7.0) [1, 38] | 28.8 (5.5) [0, 38] |
|               | Class 1 N=230 | Class 1 N=992 | Class 1 N=226 | Class 1 N=1091 |
|---------------|---------------|---------------|---------------|---------------|
| Parental Education |               |               |               |               |
| No schooling  | 147 (30.8)    | 579 (29.0)    | 203 (39.0)    | 722 (33.6)    |
| Primary schooling | 237 (49.7)    | 1055 (52.9)   | 257 (49.4)    | 1124 (52.4)   |
| Secondary schooling | 75 (15.7)     | 278 (13.9)    | 42 (8.1)      | 236 (11.0)    |
| Higher education | 18 (3.8)      | 84 (4.2)      | 18 (3.5)      | 65 (3.0)      |
| Socioeconomic status |           |               |               |               |
| Poorest       | 95 (19.8)     | 345 (17.2)    | 124 (23.8)    | 531 (24.6)    |
| Poor          | 105 (21.9)    | 378 (18.9)    | 115 (22.0)    | 449 (20.8)    |
| Median        | 87 (18.2)     | 378 (18.9)    | 99 (19.0)     | 396 (18.3)    |
| Less poor     | 73 (15.2)     | 451 (22.5)    | 105 (20.1)    | 404 (18.7)    |
| Least poor    | 119 (24.8)    | 453 (22.6)    | 79 (15.1)     | 379 (17.6)    |
| Household size |               |               |               |               |
| 1-5           | 158 (33.1)    | 539 (26.9)    | 144 (27.7)    | 559 (26.0)    |
| 6-9           | 262 (54.8)    | 1182 (59.1)   | 298 (57.4)    | 1282 (59.7)   |
| 10-31         | 58 (12.1)     | 280 (14.0)    | 77 (14.8)     | 305 (14.2)    |
| Study endpoints-baseline |           |               |               |               |
| Class 5 N=266 |               |               | Class 5 N=1035|               |
| Class 5 N=310 |               |               | Class 5 N=1083|               |
| Anemia prevalence |           |               |               |               |
| Age-sex specific | 206 (47.0)    | 867 (44.8)    | 194 (45.9)    | 920 (45.4)    |
| Severe (<70g/L) | 2 (0.5)       | 12 (0.6)      | 1 (0.2)       | 13 (0.6)      |
| Moderate (70-89 g/L) | 8 (1.8)    | 35 (1.8)      | 9 (2.1)       | 46 (2.3)      |
| Mild (90-109 g/L) | 98 (22.4)    | 432 (22.3)    | 83 (19.6)     | 435 (21.4)    |
| None (≥110 g/L) | 330 (75.3)    | 1456 (75.2)   | 330 (78.0)    | 1534 (75.6)   |
| Hemoglobin (g/L) |           |               |               |               |
| Mean (sd)     | 117.3 (13.3)  | 117.3 (12.9)  | 118.5 (13.6)  | 117.3 (13.7)  |
| P.falciparum prevalence |           |               |               |               |
| Score: 0-20  | 11.6 (6.7) [0, 20] | 11.9 (6.7) [0, 20] | 11.6 (6.8) [0, 20] | 12.3 (6.5) [0, 20] |
| Score: 0-20  | 8.5 (4.1) [0, 19] | 8.6 (4.6) [0, 19] | 7.7 (4.7) [0, 19] | 7.6 (4.4) [0, 20] |
| Score: 0-30 | Arithmetic | 2.6 (2.3) [0, 12] | 2.6 (2.4) [0, 17] | 2.6 (2.8) [0, 15] | 2.6 (2.4) [0, 12] |
|-------------|------------|------------------|------------------|------------------|------------------|
| **Class 5** |            |                  |                  |                  |                  |
| Score: 0-20 | Sustained attention | 9.8 (6.1) [0, 20] | 9.9 (6.0) [0, 20] | 9.4 (5.5) [0, 20] | 10.7 (5.7) [0, 20] |
| Score: 0-78 | Spelling   | 24.2 (11.4) [0, 52] | 28.9 (11.7) [0, 63] | 22.5 (10.7) [1, 51] | 26.7 (11.1) [1, 59] |
| Score: 0-38 | Arithmetic | 28.6 (6.2) [4, 38] | 29.6 (5.4) [0, 38] | 27.3 (6.4) [3, 38] | 28.8 (5.6) [0, 38] |

* % of non-missing children in each study group presented for categorized data, where data is continuous mean(sd) is presented.
* Not measured at baseline in the control group.
* Presented as mean(sd) [min,max]
* In class 1 sustained attention was measured by the “pencil tap test” and in class 5 sustained attention was measured by the “two digit code transmission test.”
Table S3. Results from missing data analysis for anemia. Effect of the IST intervention at 12 and 24 months follow-up on the primary health outcome of anemia for study children combined using a longitudinal, random effects regression modeling approach. Results presented (i) for all children with either 12 or 24 months follow-up measurements of the outcome (unadjusted), (ii) for those with baseline measurements of the outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis, and (iii) for those additionally with baseline measures of parental education, SES and baseline educational level (measured by baseline spelling) as further predictors of missingness.

| Prevalence of anemia¹ | Control (50 schools) | Intervention (51 schools) | Odds ratio² | p-value³ | ICC (95% CI) |
|-----------------------|----------------------|--------------------------|-------------|----------|--------------|
|                       | n (%)ᵇ | n (%)ᵇ | (95% CI) |          |              |
| **Unadjusted**        |         |         |          |          |              |
| 12-month              | 2146    | 837 (39.0%) | 2297     | 920 (40.1%) | 1.08 (0.74,1.43) | 0.758 | 0.07 (0.05,0.10) | 0.50 (0.45,0.54) |
| 24-month              | 2027    | 809 (39.9%) | 2173     | 910 (41.9%) | 1.12 (0.77,1.48) | 0.758 | 0.06 (0.04,0.08) | 0.38 (0.33,0.43) |
| **Adjusted**          |         |         |          |          |              |
| 12-month              | 2048    | 788 (38.5%) | 2142     | 858 (40.1%) | 1.09 (0.79,1.40) |          |              |              |
| 24-month              | 1935    | 765 (39.5%) | 2027     | 842 (41.5%) | 1.11 (0.80,1.42) | 0.890 | 0.06 (0.04,0.08) | 0.38 (0.33,0.43) |
| **Adjusted for predictors of missingness** | | | | | | | |
| 12-month              | 1998    | 768 (38.4%) | 2083     | 832 (39.9%) | 1.05 (0.77,1.34) | 0.789 |          |              |
| 24-month              | 1889    | 747 (39.5%) | 1969     | 820 (41.7%) | 1.09 (0.79,1.38) | 0.05 (0.03,0.07) | 0.34 (0.32,0.42) |

¹ Age-sex specific anemia was defined using age and sex corrected WHO thresholds of hemoglobin concentration: <110g/l in children under 5 years; <115g/l in children 5 to 11 years; <120g/l in females 12 years and over and males 12 to 14.99 years old; and <130g/l in males ≥ 15 years. All female adolescents are assumed to not be pregnant.

² Odds ratios (intervention/control) presented for anemia are obtained from random effects logistic regression analysis accounting for school-level clustering and repeated measures of children for the comparison of the intervention effect at 12 months to 24 months.

³ p-value for the comparison of the intervention effect at 12 months to 24 months.

Unadjusted: All children with outcome measures, not adjusted for any baseline or study design characteristics.

Adjusted: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available.
Adjusted for predictors of missingness: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available. Additionally adjusted for parental education, SES and baseline educational level as measured by baseline spelling score (standardized by subtracting year-group baseline mean and scaled by year-group sd).
Table S4. Baseline measures for study children with missing 9 months follow-up education data vs. those not missing 9 months follow-up education data across both the control and intervention groups.

| Characteristic; n (%) | CONTROL GROUP | INTERVENTION GROUP |
|-----------------------|---------------|-------------------|
|                       | Missing outcome data | Outcome available | Missing outcome data | Outcome available |
| Child characteristics  | N=265          | N=2258            | N=312              | N=2398            |
| Age                   |                |                   |                    |                   |
| Mean (sd)             | 10.0 (3.2)     | 10.1 (2.8)        | 10.5 (3.1)         | 10.3 (2.8)        |
| 5-9                   | 125 (47.2)     | 916 (40.6)        | 121 (38.8)         | 948 (39.5)        |
| 10-12                 | 71 (26.8)      | 806 (35.7)        | 91 (29.2)          | 834 (34.8)        |
| 13-20                 | 68 (26.0)      | 536 (23.7)        | 100 (32.1)         | 616 (25.7)        |
| Sex                   |                |                   |                    |                   |
| Male                  | 134 (50.6)     | 1123 (49.7)       | 157 (50.3)         | 1162 (48.5)       |
| Child sleeps under net |               |                   |                    |                   |
| Usually               | 167 (66.8)     | 1501 (67.3)       | 174 (58.6)         | 1508 (63.7)       |
| Last night            | 164 (98.2)     | 1442 (96.1)       | 169 (97.1)         | 1440 (95.5)       |
| Nutritional Status    |                |                   |                    |                   |
| Underweight           | 38 (34.9)      | 228 (26.0)        | 17 (19.5)          | 214 (24.3)        |
| Stunted               | 55 (24.6)      | 545 (23.7)        | 44 (19.2)          | 568 (25.4)        |
| Thin                  | 48 (21.4)      | 434 (20.1)        | 39 (17.0)          | 411 (18.4)        |
| Household characteristics |            |                   |                    |                   |
| Parental Education    |                |                   |                    |                   |
| No schooling          | 81 (32.5)      | 645 (29.0)        | 127 (42.8)         | 798 (33.7)        |
| Primary schooling     | 128 (51.4)     | 1164 (52.3)       | 141 (47.5)         | 1240 (52.3)       |
| Secondary schooling   | 30 (12.0)      | 323 (14.5)        | 17 (5.7)           | 261 (11.0)        |
| Socioeconomic status  |                |                   |                    |                   |
| Poor                  | 10 (22.0)      | 385 (17.2)        | 84 (28.1)          | 571 (24.0)        |
| Median                | 54 (21.6)      | 429 (19.2)        | 66 (22.1)          | 498 (20.9)        |
| Less poor             | 54 (21.6)      | 429 (19.2)        | 66 (22.1)          | 498 (20.9)        |
| Least poor            | 42 (16.8)      | 423 (18.9)        | 53 (17.7)          | 442 (18.6)        |
| Household size        |                |                   |                    |                   |
| 1-5                   | 118 (47.2)     | 1326 (59.5)       | 171 (57.6)         | 1409 (59.5)       |
| 6-9                   | 42 (16.8)      | 296 (13.3)        | 38 (12.8)          | 344 (14.5)        |
| Study endpoints-baseline |            |                   |                    |                   |
| Anemia prevalence     |                |                   |                    |                   |
| Age-sex specific      | 93 (42.9)      | 980 (45.5)        | 93 (45.2)          | 1016 (45.5)       |
| Severe (<70g/L)       | 1 (0.5)        | 13 (0.6)          | 1 (0.5)            | 13 (0.6)          |
| Moderate (70-89 g/L)  | 8 (3.7)        | 35 (1.6)          | 9 (4.1)            | 46 (2.1)          |
| Mild (90-109 g/L)     | 43 (19.8)      | 487 (22.6)        | 44 (20.3)          | 474 (21.2)        |
| None (≥110 g/L)       | 165 (76.0)     | 1621 (75.2)       | 163 (75.1)         | 1701 (76.1)       |
| Hemoglobin (g/L)      | Mean (sd)      |                    |                    |                   |
|                       | 116.6 (14.1)   | 117.4 (12.9)      | 117.5 (15.0)       | 117.5 (13.6)      |
| P.falciparum prevalence b | - - - - | 19 (9.1) | 292 (13.3) |
|--------------------------|----------|----------|-----------|
| **Class 1 c**            |          |          |           |
| Score: 0-20              | Sustained attention d | 11.0 (6.8) [0, 20] | 12.0 (6.6) [0, 20] | 12.3 (6.7) [0, 20] | 12.1 (6.6) [0, 20] |
| Score: 0-20              | Spelling  | 8.2 (4.3) [0, 19] | 8.6 (4.5) [0, 20] | 7.1 (4.2) [0, 18] | 7.7 (4.4) [0, 20] |
| Score: 0-30              | Arithmetic | 2.8 (2.6) [0, 13] | 2.5 (2.3) [0, 17] | 2.8 (2.9) [0, 13] | 2.5 (2.4) [0, 15] |
| **Class 5 c**            |          |          |           |
| Score: 0-20              | Sustained attention d | 9.8 (5.8) [0, 20] | 9.9 (6.0) [0, 20] | 9.5 (5.8) [0, 20] | 10.6 (5.6) [0, 20] |
| Score: 0-78              | Spelling  | 24.6 (11.1) [2, 52] | 28.2 (11.8) [0, 63] | 25.1 (11.2) [1, 51] | 25.9 (11.2) [1, 59] |
| Score: 0-38              | Arithmetic | 28.3 (6.6) [5, 38] | 29.5 (5.5) [0, 38] | 27.8 (7.2) [3, 38] | 28.6 (5.6) [0, 38] |

a % of non-missing children in each study group presented for categorized data, where data is continuous mean(sd) is presented.
b Not measured at baseline in the control group;
c Presented as mean(sd) [min,max]
d In class 1 sustained attention was measured by the "pencil tap test" and in class 5 sustained attention was measured by the "two digit code transmission test".
Table S5. Baseline measures for study children with missing 24 months follow-up education data vs. those not missing 24 months follow-up education data across both the control and intervention groups.

| Characteristic; n (%) | CONTROL GROUP | INTERVENTION GROUP |
|-----------------------|---------------|-------------------|
|                       | Missing outcome data | Outcome available | Missing outcome data | Outcome available |
| **Child characteristics** | N=543 | N=1980 | N=584 | N=2126 |
| **Age** | Mean (sd) | 10.5 (3.1) | 10.0 (2.8) | 10.9 (3.1) | 10.2 (2.7) |
| 5-9 | 213 (39.2) | 828 (41.8) | 202 (34.6) | 867 (40.8) |
| 10-12 | 161 (29.7) | 716 (36.2) | 167 (28.6) | 758 (35.7) |
| 13-20 | 169 (31.1) | 436 (22.0) | 215 (36.8) | 501 (23.6) |
| **Sex** | Male | 271 (49.9) | 986 (49.8) | 270 (46.2) | 1049 (49.3) |
| **Child sleeps under net** | Usually | 343 (65.2) | 1325 (67.8) | 345 (61.0) | 1337 (63.7) |
| Last night | 334 (97.4) | 1272 (96.0) | 328 (95.1) | 1281 (95.8) |
| **Nutritional Status** | Underweight | 49 (26.1) | 217 (27.2) | 37 (22.8) | 194 (24.1) |
| Stunted | 114 (23.7) | 486 (25.5) | 121 (25.0) | 491 (24.8) |
| Thin | 90 (18.7) | 392 (20.6) | 74 (15.3) | 376 (19.0) |
| **Household characteristics** | | | | |
| **Parental Education** | No schooling | 167 (31.8) | 559 (28.7) | 229 (40.4) | 696 (33.1) |
| Primary schooling | 258 (49.1) | 1034 (53.1) | 271 (47.8) | 1110 (52.9) |
| Secondary schooling | 82 (15.6) | 271 (13.9) | 46 (8.1) | 232 (11.0) |
| Higher education | 18 (3.4) | 84 (4.3) | 21 (3.7) | 62 (3.0) |
| **Socioeconomic status** | Poorest | 102 (19.4) | 338 (17.3) | 138 (24.3) | 517 (24.5) |
| Poor | 119 (22.6) | 364 (18.6) | 125 (22.0) | 439 (20.8) |
| Median | 92 (17.5) | 373 (19.1) | 110 (19.3) | 385 (18.2) |
| Less poor | 86 (16.3) | 438 (22.4) | 109 (19.2) | 400 (18.9) |
| Least poor | 128 (24.3) | 444 (22.7) | 87 (15.3) | 371 (17.6) |
| **Household size** | 1-5 | 163 (31.0) | 534 (27.3) | 152 (26.9) | 551 (26.3) |
| 6-9 | 293 (55.7) | 1175 (60.9) | 335 (58.9) | 1245 (59.3) |
| 10-31 | 70 (13.3) | 268 (13.7) | 79 (14.0) | 303 (14.4) |
| **Study endpoints-baseline** | | | | |
| **Anemia prevalence** | Age-sex specific | 213 (44.9) | 860 (45.3) | 211 (44.8) | 903 (45.6) |
| Severe (<70g/L) | 2 (0.4) | 12 (0.6) | 1 (0.2) | 13 (0.7) |
| Moderate (70-89 g/L) | 10 (2.1) | 33 (1.7) | 9 (1.9) | 46 (2.3) |
| Mild (90-109 g/L) | 104 (21.9) | 426 (22.4) | 91 (19.3) | 427 (21.6) |
| Hemoglobin (g/L) | Mean (sd) | 358 (75.5) | 1428 (75.2) | 370 (78.6) | 1494 (75.5) |
|-----------------|-----------|------------|-------------|------------|-------------|
| P. falciparum prevalence | | 117.4 (13.4) | 117.3 (12.9) | 118.7 (13.6) | 117.2 (13.7) |
| Class 1 | Score: 0-20 | Sustained attention | 11.8 (6.6) [0, 20] | 11.9 (6.7) [0, 20] | 11.9 (6.6) [0, 20] | 12.2 (6.6) [0, 20] |
| | Score: 0-20 | Spelling | 8.5 (4.2) [0, 19] | 8.6 (4.6) [0, 19] | 7.6 (4.6) [0, 19] | 7.7 (4.4) [0, 20] |
| | Score: 0-30 | Arithmetic | 2.5 (2.3) [0, 12] | 2.6 (2.4) [0, 17] | 2.6 (2.7) [0, 13] | 2.6 (2.4) [0, 15] |
| Class 5 | Score: 0-20 | Sustained attention | 9.9 (6.1) [0, 20] | 9.9 (6.0) [0, 20] | 9.6 (5.6) [0, 20] | 10.7 (5.7) [0, 20] |
| | Score: 0-78 | Spelling | 25.4 (11.6) [0, 53] | 28.6 (11.7) [0, 63] | 23.1 (11.1) [1, 59] | 26.6 (11.1) [1, 59] |
| | Score: 0-38 | Arithmetic | 28.7 (6.3) [4, 38] | 29.5 (5.3) [0, 38] | 27.7 (6.3) [3, 38] | 28.8 (5.6) [0, 38] |

* % of non-missing children in each study group presented for categorized data, where data is continuous mean(sd) is presented.

Not measured at baseline in the control group;

Presented as mean(sd) [min,max]

In class 1 sustained attention was measured by the “pencil tap test” and in class 5 sustained attention was measured by the “two digit code transmission test”.

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Table S6. Results from missing data analysis for sustained attention. Effect of the IST intervention at 9 and 24 months follow-up on sustained attention outcomes for younger (class 1) and older (class 5) children combined using a longitudinal, random effects regression modeling approach. Results presented (i) for all children with either 9 or 24 months follow-up measurements of the outcome (unadjusted), (ii) for those with baseline measurements of the outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis, and (iii) for those additionally with baseline measures of parental education, SES and baseline educational level (measured by baseline spelling) as further predictors of missingness.

| Sustained attention (score: 0-20) | Control Mean (SD) | Intervention Mean (SD) | Mean difference \( d \) (95% CI) | \( p \)-value \( ^e \) | ICC (95% CI) |
|-----------------------------------|-------------------|------------------------|---------------------------------|-----------------|-------------|
|                                   | (50 schools)       | (51 schools)           |                                 |                 |             |
| Class 1a                          | Mean (SD) \(^a\)  | Mean (SD) \(^a\)       |                                 | \( d \)         |             |
| Unadjusted                        |                   |                        |                                 |                 |             |
| 9-months                          | 1070  8.48 (3.63) | 1162  8.43 (3.76)      | -0.05 (-0.53, 0.44)             | 0.409           | 0.04 (0.02, 0.06) 0.17 (0.13, 0.22) |
| 24-months                         | 960  13.45 (5.15) | 1059  13.20 (4.96)     | -0.25 (-0.75, 0.24)             | 0.311           | 0.03 (0.02, 0.05) 0.13 (0.09, 0.18) |
| Adjusted                          |                   |                        |                                 |                 |             |
| 9-months                          | 1030  8.52 (3.65) | 1144  8.43 (3.77)      | -0.16 (-0.61, 0.30)             | 0.311           | 0.03 (0.02, 0.05) 0.13 (0.09, 0.18) |
| 24-months                         | 923  13.49 (5.15) | 1041  13.18 (4.96)     | -0.41 (-0.88, 0.06)             | 0.385           | 0.02 (0.01, 0.04) 0.12 (0.08, 0.17) |
| Adjusted for predictors of missingness |                   |                        |                                 |                 |             |
| 9-months                          | 1013  8.54 (3.67) | 1118  8.43 (3.77)      | -0.02 (-0.43, 0.46)             |                 |             |
| 24-months                         | 908  13.49 (5.16) | 1017  13.19 (5.00)     | -0.21 (-0.67, 0.26)             | 0.385           | 0.02 (0.01, 0.04) 0.12 (0.08, 0.17) |
| Class 5c                          | Mean (SD) \(^a\)  | Mean (SD) \(^a\)       |                                 |                 |             |
| Unadjusted                        |                   |                        |                                 |                 |             |
| 9-months                          | 1180  13.38 (5.45) | 1231  13.35 (5.13)     | -0.07 (-0.65, 0.51)             |                 |             |
| 24-months                         | 1007  14.22 (4.90) | 1052  14.66 (5.13)     | 0.31 (-0.29, 0.91)              | 0.083           | 0.04 (0.03, 0.07) 0.52 (0.49, 0.55) |
|               | 9-months |             | 24-months |             |               |             |               |               |
|---------------|----------|-------------|-----------|-------------|---------------|-------------|---------------|---------------|
|               | 1178     | 13.38 (5.45)| 1221      | 13.40 (5.10)| -0.14 (-0.65,0.37)|             |               |               |
| Adjusted      |          |             |           |             |               |             |               |               |
| 24-months     | 1006     | 14.21 (4.90)| 1044      | 14.70 (5.10)| 0.19 (-0.33,0.72)| 0.122       | 0.04 (0.03,0.07)| 0.40 (0.36,0.44)|
|               |          |             |           |             |               |             |               |               |
| Adjusted for predictors of missingness |          |             |           |             |               |             |               |               |
| 9-months      | 1141     | 13.39 (5.42)| 1203      | 13.40 (5.10)| -0.02 (-0.54,0.51)|             |               |               |
| 24-months     | 971      | 14.24 (4.85)| 1028      | 14.69 (4.58)| 0.29 (-0.25,0.84)| 0.160       | 0.05 (0.03,0.07)| 0.37 (0.34,0.42)|

- Mean score and sd at follow-up.
- Pencil tap test was conducted at baseline and single digit code transmission task was conducted at 9 and 24 months follow-ups.
- Double digit code transmission was conducted at baseline and both follow up visits.
- Mean difference (intervention-control) presented for continuous outcomes (scores on attention task) and are obtained from random effects regression analysis accounting for school-level clustering and repeated measures on children.
- P-value for the comparison of the intervention effect at 12 months to 24 months.

**Unadjusted**: All children with outcome measures, not adjusted for any baseline or study design characteristics.

**Adjusted**: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available.

**Adjusted for predictors of missingness**: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available. Additionally adjusted for parental education, SES and baseline educational level as measured by baseline spelling score (standardized by subtracting year-group baseline mean and scaled by year-group sd).
Table S7: Results from missing data analysis for spelling. Effect of the IST intervention at 9 and 24 months follow-up on spelling outcomes for younger (class 1) and older (class 5) children combined using a longitudinal, random effects regression modeling approach. Results presented (i) for all children with either 9 or 24 months follow-up measurements of the outcome (unadjusted), (ii) for those with baseline measurements of the outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis, and (iii) for those additionally with baseline measures of parental education, SES and baseline educational level (measured by baseline spelling) as further predictors of missingness.

| Spelling score | Control (50 schools) | Intervention (51 schools) | Mean difference \(^d\) (95% CI) | p-value \(^a\) | ICC (95% CI) |
|----------------|----------------------|---------------------------|----------------------------------|--------------|--------------|
|                | Class 1 \(^b\)       |                           |                                  |              |              |
| Unadjusted     |                      |                           |                                  |              |              |
| 9-months       | 1068                 | 11.70 (4.59)              | 1162                             | 10.47 (4.57) | -1.24 (-2.00,-0.48) |
| 24-months      | 961                  | 12.03 (3.05)              | 1062                             | 11.04 (3.49) | -0.98 (-1.74,-0.21) |
| Adjusted       |                      |                           |                                  |              |              |
| 9-months       | 1060                 | 11.69 (4.59)              | 1133                             | 10.49 (4.58) | -0.79 (-1.28,-0.30) |
| 24-months      | 954                  | 12.02 (3.05)              | 1036                             | 11.04 (3.50) | -0.54 (-1.04,-0.05) |
| Adjusted for predictors of missingness | | | | | |
| 9-months       | 1049                 | 11.70 (4.59)              | 1121                             | 10.49 (4.58) | -0.75 (-1.23,-0.27) |
| 24-months      | 944                  | 12.05 (3.03)              | 1025                             | 11.03 (3.50) | -0.54 (-1.02,-0.05) |
| Class 5 \(^c\) |                      |                           |                                  |              |              |
| Unadjusted     |                      |                           |                                  |              |              |
| 9-months       | 1169                 | 31.34 (12.61)             | 1223                             | 28.73 (12.36) | -2.69 (-5.10,-0.27) |
| 24-months      | 1010                 | 35.28 (12.91)             | 1060                             | 33.97 (12.79) | -1.70 (-4.13,0.73) |

\(^a\) Mean (SD), \(^b\) Unadjusted, \(^c\) Adjusted for predictors of missingness
Adjusted for predictors of missingness

|                  | Adjusted        | Adjusted for predictors of missingness |
|------------------|-----------------|----------------------------------------|
|                  | Unadjusted      | Adjusted                                |
|                  | Adjusted        | Adjusted for predictors of missingness  |
| 9-months         | 1154 31.37 (12.60) 1214 28.76 (12.34) -0.28 (-1.16,0.60) | 1131 31.49 (12.69) 1198 28.69 (12.36) -0.18 (-1.07,0.70) |
| 24-months        | 996 35.33 (12.85) 1052 34.04 (12.75) 0.68 (0.22,1.58) 0.001 0.08 (0.06,0.12) 0.43 (0.40,0.47) | 974 35.57 (12.81) 1037 33.98 (12.77) 0.73 (-0.18,1.63) 0.003 0.08 (0.06,0.12) 0.43 (0.40,0.47) |

*a* Mean score and sd at follow-up based on the data

*b* The same class 1 spelling task was given at baseline, 9 and 24 months follow-ups, with different words used for the 24 month follow-up and was scored 0-20.

*c* The same class 5 spelling task was given at baseline, 9 and 24 months follow-ups, with different words used for the 24 month follow-up and was scored 0-78.

*d* Mean difference (intervention-control) presented for continuous outcomes (scores on spelling task) and are obtained from random effects regression analysis accounting for school-level clustering and repeated measures on children.

*e* p-value for the comparison of the intervention effect at 12 months to 24 months

Unadjusted: All children with outcome measures, not adjusted for any baseline or study design characteristics.

Adjusted: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available.

Adjusted for predictors of missingness: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available. Additionally adjusted for parental education, SES and baseline educational level as measured by baseline spelling score (standardized by subtracting year-group baseline mean and scaled by year-group sd).
Table S8. Sensitivity analyses considering transfers across the study period. Effect of the IST intervention at 12 and 24 months follow-up on health outcomes for study children. Results presented (i) for all children with either 12 or 24 months follow-up measurements of the outcome (unadjusted) with children who transferred schools excluded and (ii) for those with baseline measurements of each outcome and accounting for age, sex and stratification effects as the primary pre-specified analysis with children who transferred schools excluded.

| Outcome               | Control   | Intervention | Risk ratio<sup>b</sup> | p-value | Cluster-size; range (average) |
|-----------------------|-----------|--------------|-------------------------|---------|------------------------------|
|                       | (50 schools) | (51 schools) | (95% CI)                |         |                              |
|                       | n (%)<sup>a</sup> | n (%)<sup>a</sup> |                        |         |                              |
| 12 month follow-up    | N=2439 | N=2574 | | | |
| Prevalence of anemia<sup>c</sup> | | | | | |
| Unadjusted            | 2117 | 827 (39.1%) | 2255 | 906 (40.2%) | 1.03 (0.91,1.16) | 0.640 | 15-54 (43.3) |
| Adjusted              | 2023 | 780 (38.6%) | 2106 | 847 (40.2%) | 1.02 (0.93,1.13) | 0.670 | 15-54 (40.9) |
| Prevalence of P.falciparum | | | | | |
| Unadjusted            | 2078 | 300 (14.4%) | 2235 | 243 (10.9%) | 0.76 (0.49,1.19) | 0.234 | 11-54 (42.7) |
| Adjusted<sup>d</sup>  | 2078 | 300 (14.4%) | 2235 | 243 (10.9%) | 0.72 (0.46,1.11) | 0.139 | 11-54 (42.7) |
| 24 months follow-up   | N=2362 | N=2417 | | | |
| Prevalence of anemia<sup>c</sup> | | | | | |
| Unadjusted            | 1929 | 770 (39.9%) | 1999 | 843 (42.2%) | 1.06 (0.91,1.22) | 0.463 | 15-52 (39.3) |
| Adjusted              | 1845 | 728 (39.5%) | 1862 | 780 (41.9%) | 1.01 (0.90,1.12) | 0.920 | 14-52 (37.1) |
| Prevalence of P.falciparum | | | | | |
| Unadjusted            | 1908 | 162 (8.5%) | 1972 | 239 (12.2%) | 1.42 (0.83,2.43) | 0.206 | 15-52 (38.8) |
| Adjusted<sup>d</sup>  | 1908 | 162 (8.5%) | 1972 | 239 (12.2%) | 1.49 (0.86,2.57) | 0.154 | 15-52 (38.8) |
N = number of children eligible for follow up (not withdrawn or deceased)

* Number and percentage with outcome

b Risk ratios presented for binary outcomes (anemia & *P. falciparum* prevalence) and are obtained from GEE analysis accounting for school-level clustering.

c Age-sex specific anemia was defined using age and sex corrected WHO thresholds of hemoglobin concentration: <110g/l in children under 5 years; <115g/l in children 5 to 11 years; <120g/l in females 12 years and over and males 12 to 14.99 years old; and <130g/l in males ≥ 15 years. All female adolescents are assumed to not be pregnant

d Not including baseline *P. falciparum* prevalence

Unadjusted: All children with outcome measures, not adjusted for any baseline or study design characteristics.

Adjusted: for baseline age, sex, school mean exam score and literacy group (to account for stratification) and baseline measure of the outcome, where available
Table S9. Analysis stratified by categories of *P. falciparum* prevalence at baseline. Effect of the IST intervention at 12 and 24 months follow-up on the prevalence of anemia, by baseline prevalence category of *P. falciparum* (control school prevalence estimated using 12 month follow-up data) with adjustment for age, sex and stratification effects.

| Prevalence of anemia | Control (50 schools) | Intervention (51 schools) | Risk ratio<sup>c</sup> | p-value |
|----------------------|----------------------|---------------------------|------------------------|---------|
|                      | n (%)<sup>b</sup>    | n (%)<sup>b</sup>         |                        |         |
| **Follow-up 12 months** |                     |                           |                        |         |
| Baseline % *P. falciparum*<sup>a</sup> |                     |                           |                        |         |
| <5%                  | 787                  | 265 (33.7%)              | 751                    | 270 (36.0%) | 1.01 (0.84,1.23) | 0.578 |
| 5-19.9%             | 606                  | 220 (36.3%)              | 858                    | 358 (41.7%) | 1.09 (0.95,1.26) | 0.578 |
| ≥20%                | 655                  | 303 (46.3%)              | 533                    | 230 (43.2%) | 0.99 (0.87,1.13) |       |
| **Follow-up 24 months** |                     |                           |                        |         |
| Baseline % *P. falciparum*<sup>a</sup> |                     |                           |                        |         |
| <5%                  | 740                  | 264 (35.7%)              | 710                    | 243 (34.2%) | 0.95 (0.78,1.16) |       |
| 5-19.9%             | 572                  | 226 (39.5%)              | 803                    | 364 (45.3%) | 0.99 (0.86,1.14) | 0.840 |
| ≥20%                | 623                  | 275 (44.1%)              | 514                    | 235 (45.7%) | 1.03 (0.86,1.24) |       |

N=numbers not withdrawn or died by the time of follow-up.
<sup>a</sup> Control school *P. falciparum* prevalence was estimated using 12 month follow-up data.
<sup>b</sup> Number and percentage with outcome.
<sup>c</sup> Risk ratios presented are obtained from GEE analysis accounting for school-level clustering and baseline outcome (anemia).
Table S10. Analysis stratified by number of AL treatments received. Effect of the IST intervention at 12 and 24 months follow-up within the IST intervention group by number of positive results and subsequent treatments received at the individual level.

| Prevalence of anemia | Intervention (51 schools) | Risk ratio<sup>d</sup> (95% CI) | p-value |
|----------------------|--------------------------|-------------------------------|---------|
| **Follow-up 12 months** |                          |                               |         |
| No. treatments received<sup>c</sup> | N<sup>a</sup> | n (%)<sup>b</sup> | 0 | 0.839 |
| 0 | 1417 | 545 (38.5%) | 0 | 0.99 (0.90, 1.09) | 0.839 |
| 1 | 588 | 241 (41.0%) | 1.04 (0.91, 1.19) |         |
| 2-3 | 288 | 131 (45.5%) | 1.04 (0.91, 1.19) |         |
| **Follow-up 24 months** |                          |                               |         |
| No. treatments received<sup>c</sup> | N=2169 | 546 (40.9%) | 0 |         |
| 0 | 1336 | 546 (40.9%) | 0 | 0.96 (0.88, 1.05) | 0.470 |
| 1-2 | 563 | 233 (41.4%) | 1.03 (0.88, 1.21) |         |
| 3-5 | 270 | 129 (47.8%) | 1.03 (0.88, 1.21) |         |

<sup>a</sup> Number of children receiving by the number of visits at which they required and received treatment for *Plasmodium* infection

<sup>b</sup> Number and percentage of children with anemia at follow-up

<sup>c</sup> At 12 month follow-up the maximum possible treatments was three as three IST rounds had been completed. By the 24 month follow-up the maximum possible treatments was five as five IST rounds had been completed

<sup>d</sup> Risk ratios presented are obtained from GEE analysis accounting for school-level clustering and baseline outcome (anemia).
| Section/Topic | Item No | Standard Checklist item | Extension for cluster designs | Section and paragraph (P) No * |
|--------------|---------|-------------------------|-------------------------------|-------------------------------|
| Title and abstract | 1a | Identification as a randomized trial in the title | Identification as a cluster randomized trial in the title | Title |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | See table 2 | Abstract |
| Introduction | 2a | Scientific background and explanation of rationale | Rationale for using a cluster design | Introduction - Paragraphs 1&2 Methods – Paragraph 8 |
| | 2b | Specific objectives or hypotheses | Whether objectives pertain to the cluster level, the individual participant level or both | Introduction - Paragraph 2 Methods – Paragraph 5 |
| Methods | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | Definition of cluster and description of how the design features apply to the clusters | Methods – Paragraphs 5 & 8 Figure 2 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | n/a | |
| Participants | 4a | Eligibility criteria for participants | Eligibility criteria for clusters | Methods – Paragraphs 4 & 6 |
| | 4b | Settings and locations where the data were collected | Methods – Paragraphs 3 & 4 Figure 1 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | Whether interventions pertain to the cluster level, the individual participant level or both | Methods – Paragraph 11 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | Whether outcome measures pertain to the cluster level, the individual participant level or both | Methods – Paragraphs 5, 6, 13, 14, 15 & 16 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | N/A | |
| Sample size | 7a | How sample size was determined | Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intraclass correlation (ICC or k), and an indication of its uncertainty | Methods – Paragraph 7 |
| Section | Question | Additional Information |
|---------|----------|------------------------|
| Randomization | When applicable, explanation of any interim analyses and stopping guidelines | N/A |
| Sequence generation | Method used to generate the random allocation sequence | Methods – paragraph 8 |
| | Type of randomization; details of any restriction (such as blocking and block size) | Details of stratification or matching if used | Methods – paragraph 8 |
| Allocation concealment mechanism | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both | Methods – paragraphs 5, 6, 7 & 8 |
| Implementation | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | Replace by 10a, 10b and 10c |
| | Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions | Methods – paragraph 8 |
| | Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling) | Methods – paragraphs 6 & 7 |
| | From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomization | Methods – paragraph 2 |
| Blinding | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | Non-blinded trial |
| | If relevant, description of the similarity of interventions | Discussion – Paragraph 8 |
| Statistical methods | Statistical methods used to compare groups for primary and secondary outcomes | How clustering was taken into account | Methods – paragraphs 18, 19 & 20 |
| | Methods for additional analyses, | Methods – paragraphs 20 & 21 |
such as subgroup analyses and adjusted analyses

Results

| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome | For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analyzed for the primary outcome | Figure 3 |
|--------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------|
|                                                        | 13b | For each group, losses and exclusions after randomization, together with reasons | For each group, losses and exclusions for both clusters and individual cluster members | Results – Paragraphs 4 & 5 Discussion – Paragraph 2 Figure 3 |
| Recruitment                                            | 14a | Dates defining the periods of recruitment and follow-up | Baseline characteristics for the individual and cluster levels as applicable for each group | Methods – Paragraphs 6 & 13 Results – Paragraphs 1, 4 & 5 Figure 3 |
|                                                        | 14b | Why the trial ended or was stopped | | |
| Baseline data                                          | 15  | A table showing baseline demographic and clinical characteristics for each group | Baseline characteristics for the individual and cluster levels as applicable for each group | Results – Paragraphs 1 & 2 Table 1 |
| Numbers analysed                                       | 16  | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | For each group, number of clusters included in each analysis | Table 3 |
| Outcomes and estimation                                | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome | Tables 1, 3, 4 and 5 Results – Paragraphs 7 & 8 |
|                                                        | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | | Tables 3, 4 and 5 |
| Ancillary analyses                                     | 18  | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | | Tables S1, S2, S3, S4, S5, S6, S7, S8, S9 and S10 |
| Harms                                                  | 19  | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | | Results – Paragraphs 8 & 9 |
| Discussion                                             |     | | | |
| Limitations                                            | 20  | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | | Discussion – Paragraphs 3, 4, 5 & 7 |
| Generalizability                                       | 21  | Generalizability (external validity, applicability) of the trial findings | Generalizability to clusters and/or individual participants (as relevant) | Discussion – Paragraph 6 Conclusion |
| Interpretation                                         | 22  | Interpretation consistent with | | |
results, balancing benefits and harms, and considering other relevant evidence

## Discussion

Paragraphs 2 to 7

## Conclusion

| Other information | 23 | Registration number and name of trial registry |
|-------------------|----|-----------------------------------------------|
| **Registration**  |  | Abstract                                      |
| **Protocol**      | 24 | Where the full trial protocol can be accessed, if available |
| **Funding**       | 25 | Sources of funding and other support (such as supply of drugs), role of funders |
Table 2: Extension of CONSORT for abstracts to reports of cluster randomized trials

| Item                        | Standard Checklist item                                      | Extension for cluster trials                                      | Included |
|-----------------------------|--------------------------------------------------------------|--------------------------------------------------------------------|----------|
| **Title**                   | Identification of study as randomized                       | Identification of study as cluster randomized                       | Y        |
| **Trial design**            | Description of the trial design (e.g. parallel, cluster, non-inferiority) |                                                                    | Y        |
| **Methods**                 |                                                              |                                                                    |          |
| **Participants**            | Eligibility criteria for participants and the settings where the data were collected | Eligibility criteria for clusters                                  | Y        |
| **Interventions**           | Interventions intended for each group                        |                                                                    | Y        |
| **Objective**               | Specific objective or hypothesis                             | Whether objective or hypothesis pertains to the cluster level, the individual participant level or both | Y        |
| **Outcome**                 | Clearly defined primary outcome for this report              | Whether the primary outcome pertains to the cluster level, the individual participant level or both | Y        |
| **Randomization**           | How participants were allocated to interventions              | How clusters were allocated to interventions                       |          |
| **Blinding (masking)**      | Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment |                                                                    | Y        |
| **Results**                 |                                                              |                                                                    |          |
| **Numbers randomized**      | Number of participants randomized to each group              | Number of clusters randomized to each group                        |          |
| **Recruitment**             | Trial status                                                 |                                                                    |          |
| **Numbers analyzed**        | Number of participants analyzed in each group                | Number of clusters analyzed in each group                          | Y        |
| **Outcome**                 | For the primary outcome, a result for each group and the estimated effect size and its precision | Results at the cluster or individual participant level as applicable for each primary outcome | Y        |
| **Harms**                   | Important adverse events or side effects                      |                                                                    | NA       |
| **Conclusions**             | General interpretation of the results                        |                                                                    | Y        |
| **Trial registration**      | Registration number and name of trial register                |                                                                    | Y        |
| **Funding**                 | Source of funding                                            |                                                                    | Y        |
Protocol S1.

1. **Title of project**

Impact of malaria prevention on health and education in Kenyan schoolchildren

2. **Investigators and Institutional Affiliations**

**Principal investigator:**
Dr. Simon Brooker

**Co-investigators:**
Dr. Joseph Kiambo Njagi
Prof. Benson Estambale
Dr. Charles Mwandawiro
Dr. Siân Clarke
Dr Dr. Matthew Jukes
Dr. Margaret Dubeck
Mr George Okello
Dr, Caroline Jones

1 KEMRI/Wellcome Trust Collaborative Programme, Nairobi, Kenya
2 Division of Malaria Control, Ministry of Public Health and Sanitation, Nairobi, Kenya
3 Institute of Tropical and Infectious Diseases, University of Nairobi, Kenya
4 ESACIPAC, Kenya Medical Research Institute, Nairobi, Kenya
5 London School of Hygiene and Tropical Medicine, UK
6 Harvard University, USA
7 KEMRI/Wellcome Trust Collaborative Programme, Kilifi, Kenya

*CVs of non-KEMRI staff are attached (Appendix 1)*

3. **Abstract**

The Government of Kenya is committed to improving the education of the country’s children and recognizes the importance of child health for educational achievement. While malaria represents one of the main health problems afflicting Kenyan schoolchildren, the evidence base for policy development and program implementation for school-based malaria control remains inadequate. A recent study in western Kenya showed that delivering intermittent preventive treatment to schoolchildren improved rates of anemia and classroom concentration, but did not improve school performance. This study aims to (i) investigate the impact of a related malaria prevention strategy, intermittent screening, and treatment, on health and education among schoolchildren in a different malaria transmission setting and (ii) determine the interaction between health and improved literacy instruction. The study will be undertaken in 100 randomly selected primary schools in Kwale District. Intermittent screening and treatment will consist of all children being screened using rapid diagnostic tests for malaria once during each school term (thrice yearly). Children (with or without malaria symptoms) found to be rapid diagnostic test-positive will be treated with artemisinin-based combination therapy. Screening and treatment will be administered by district health workers. The education intervention will involve a program of training for primary school teachers to improve literacy instruction. The study is designed to detect a 25 percent reduction in anemia and an improvement of 0.2 standard deviations in mathematics and literacy tests. Additional outcomes will be measured, including malaria parasitaemia, classroom attention, and school attendance. Health and educational outcomes will be assessed before intervention and twelve and twenty-four months later. Information will also be collected on the in-vivo parasitological efficacy of treatments and the cost-effectiveness of intervention. The findings of this study will provide critical information on the effectiveness of interventions to reduce the health and education burden of malaria among school-aged children.
4. Background

Malaria poses an enormous public health burden among the population of Kenya, and several donors are supporting the up-scaling of currently available malaria interventions. Typically, these efforts focus on children under five years and pregnant women because they bear the brunt of morbidity and mortality. However, older children, including those attending school, are also at risk of mortality and morbidity (Lalloo 2006). In addition, malaria greatly contributes to school absenteeism, poor cognition, learning and school performance (Brooker et al., 2000; Holding & Snow, 2001; Lalloo, 2006).

Despite this burden among schoolchildren, there is currently no consensus as to the appropriate approach to malaria control in schools, with relevant intervention strategies likely to vary according to patterns of malaria transmission (Brooker et al., 2008). A promising school-based intervention strategy, already proven effective for improving the health of women in pregnancy, is intermittent preventive treatment (IPT). In a recent study in western Kenya, the mass administration of a full therapeutic course of an anti-malarial drug to schoolchildren once a term, irrespective of infection status, dramatically reduced malaria parasitaemia, almost halved the rates of anemia, and significantly improved cognitive ability (Clarke et al. 2008; Temperley et al., 2008). The withdrawal in Kenya in 2009 of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) from use means that these drugs can no longer be used for IPT. An alternative approach is intermittent screening and treatment (IST), a malaria prevention strategy recently identified in the Kenyan National Malaria Strategy, 2009-2017 as a possible school-based strategy in the newly launched Malaria Free School Initiative.

The proposed study will investigate the health and educational impact of school-based IST in a different epidemiological setting in Kenya, where other important contributors to anemia in school-aged children, including poor nutrition and helminth infections, are important. In addition, the study will investigate a number of scientific and operational issues which generate valuable evidence to assist in the formulation of policy recommendations for Kenya and for Sub-Saharan Africa.

a) Malaria in schoolchildren

Although all-cause mortality rates are lowest among school-age children, it is estimated that malaria causes up to 50% of all deaths in this age group in Africa (Snow et al., 2003). Morbidity studies undertaken in western Kenya suggest that between 20% to 50% of schoolchildren living in areas of stable transmission experience clinical malaria attacks each year (Clarke et al., 2004). During malaria epidemics, the incidence of malaria in schoolchildren in areas of unstable transmission may be six times higher than in areas of stable transmission (Clarke et al., 2004). Malaria (both clinical and asymptomatic malaria) is also a major cause of anemia among school-age children (Kurtzhals et al., 1999), and efforts to control malaria among this age group can dramatically improve hemoglobin levels (Geerligs, Brabin, & Eggelte, 2003).

b) Educational impact of malaria

In Kenya, primary schoolchildren miss 11% of school days per year because of malaria, and secondary schoolchildren 4% of school days (Leighton & Foster, 1993), equivalent to 4 to 10 million schooldays lost annually (Brooker et al. 2000). Evidence from Sri Lanka found that school performance is related to the cumulative impact of previous malaria attacks (Fernando et al., 2003a) and that weekly chemoprophylaxis with chloroquine improved school examination scores (Fernando et al., 2003b). This impact of malaria was mediated, at least in part, by children’s absence from school due to clinical malaria, and it remains unclear from this study whether malaria prevention improved learning processes in the classroom.

In a recent study in western Kenya (Clarke et al. 2008) we examined the cognitive processes involved in learning and found that children’s sustained attention was improved by IPT. However, this improvement was not translated into improved education achievement over the 12 month course of the study. Possible explanations for this finding are short follow-up (one year) or that children were not given the educational resources (such as textbooks) or a sufficient period of effective instruction to learn effectively during the time course of the study. It is highly plausible that the improved sustained attention we observed in our first study would translate into improved educational achievement, particularly in the early grades of school. Recent evidence (Blair & Razza, 2007) suggests that executive function skills, such as regulation and attention, are particularly important for early achievement. To achieve a measurable impact on education, it may also be necessary to improve teaching methods in order to capitalize on any improvements in health status of schoolchildren following malaria control.

In the proposed study we will follow children for a longer period of time (at least two years) and will also conduct an intervention to improve the quality and quantity of literacy instruction. This will help ensure that children have the opportunity to apply improved cognitive skills and to learn effectively. It will also give us the opportunity to study the interaction between literacy instruction and malaria prevention to investigate whether enhanced instruction is more effective when children are healthier, and to study the cognitive processes by which this interaction takes place. The role of reading abilities and the teaching methods to develop them is recognized for promoting student success and continual enrollment in school (Jimerson et al., 2000; NICHD, 2000).

c) Literacy development

As in many countries, Kenyan students begin to learn to read in their first year of schooling. Yet, about half of Kenyan students who enter primary school drop out before they reach grade 8 (Muthwii, 2004). The drop-out rate could be partially due to low performance in literacy skills (Nzomo et al., 2001).

Kenyan government policy does not mandate that a single teaching method should be used to teach reading (MOEST, 2001). Instead, the policy suggests that the teaching methods should meet the students’ learning needs and the objective for the lesson (Conmeyras & Inyega, 2007). However, the current approach does not help all enrolled students to learn to read. Nzomo et al. (2001) concluded that about 35 percent of Kenyan students did not reach the designated minimum mastery level of reading and about 77 percent did not reach the desirable level of reading. An intervention to improve the quality of classroom instruction will be designed to ensure that students benefit from literacy instruction that is understood to promote reading acquisition.
Evidence suggests that the critical components of successful literacy acquisition can be taught so that students learn to read more efficiently (Adams, 1990; August & Shanahan, 2006; Snow et al., 1998). When teachers develop their students’ oral language skills (e.g., phonological awareness & vocabulary) and teach the relationship between letters and sounds in a systematic and explicit fashion, their students have the foundation for successful word recognition and reading comprehension. Kenyan teachers will be provided with in-service to support their delivery of these foundational literacy skills as well as their assessment of these skills in order to optimize student learning.

5. Justification for Study
The Government of Kenya is committed to improving the education of its children, and recognizes the importance of child health for educational achievement. While malaria represents one of the main health problems afflicting Kenyan schoolchildren, the evidence base for policy development and program implementation for school-based malaria control remains inadequate. A recent proof-of-principle trial in western Kenya has demonstrated the potential of delivering intermittent preventive treatment (IPT) to schoolchildren in order to improve their health and education. In light of the promising results from this study, it is important to further investigate the benefits of malaria prevention in schools. A change in drug policy in Kenya means that IPT with SP and AQ is no longer a viable strategy, but that there is an important need to evaluate IST, as outlined in the revised National Malarial Strategy, 2009-2017. There is also the need to better understand the educational benefits of malaria prevention before clear policy recommendations can be made. This involves assessing the impact of the alternative strategy of IST on outcomes, such as children's ability to read, which have clear relevance to the aims of education systems. It also involves assessing the extent to which IST increases the effectiveness of improved classroom instruction. The current study will explore whether it is necessary to improve teaching methods in order to capitalize on any improvements in health status of schoolchildren following malaria control. This understanding will yield important information for both health and educational planners as they plan malaria control in school.

6. Null hypothesis
School-based malaria control using intermittent screening and treatment will not reduce rates of anemia or improve educational outcomes in Kenyan schoolchildren, when compared to a placebo.

In addition, a program of training for primary school teachers to improve literacy instruction will not improve literacy rates and there will be no interaction between the malaria intervention and the education intervention, such that learning will not be improved when teaching is effective and children are healthy.

7. Objectives

a) Overall objective:
To evaluate the impact of school-based malaria intervention using intermittent screening and treatment (IST) to reduce rates of anemia among schoolchildren and hence improve classroom attention, school attendance and educational achievement of children in school.

b) Specific objectives:

1. To evaluate the efficacy of intermittent screening and treatment (IST) in improving hemoglobin concentration of schoolchildren.

2. To evaluate the efficacy of IST in reducing rates of asymptomatic malaria parasitaemia of schoolchildren.

3. To evaluate the efficacy of IST in improving classroom attention, school attendance, and educational achievement of children in school.

4. To evaluate the impact of a program of training for primary school teachers to enhance literacy instruction in improving literacy rates of schoolchildren.

5. To determine whether malaria and education interventions work synergistically together, such that learning is improved only effective teaching is effective and children are healthy to benefit from it.

6. To analyze the cost-effectiveness of IST in improving anemia and education.

8. Design and Methodology

i) General Study design
This study will be a factorial-design, cluster-randomized, to assess the impact of IST and enhanced literacy instruction by teachers on the health and educational achievement of healthy schoolchildren. This study is one of two studies investigating the health and educational impact of malaria control, with a parallel study planned in Senegal, where malaria transmission is intense but highly seasonal.

The target population in this study includes children attending primary schools in Kenya. The accessible population includes the children attending the participating primary schools in standards 1-7 in Kwale district. The unit of analysis is the school. Schools will be randomized to one of four groups, receiving either the IST intervention alone, the education intervention alone, the IST and education interventions combined, or neither intervention. The first two arms would evaluate the impact of IST. The final two arms would investigate the hypothesis that IST helps children benefit from improved quality of education. Health and educational outcomes will be assessed before intervention and twelve and twenty four months later. The impact
of each intervention will be estimated for education outcomes and health outcomes in separate multiple regression models. An interaction term will be included to identify any synergistic effects between the two interventions.

The survey data will be collected over two years – see section 10. Development and testing of survey instruments will take place in 2008. Baseline data collection and intervention activities will commence in January 2009, with follow-up surveys planned in 2010 and 2011. The study will be conducted by the Kenya Medical Research Institute in collaboration with the Division of Malaria Control in the Ministry of Public Health and Sanitation, University of Nairobi, the London School of Hygiene and Tropical Medicine, and Harvard University.

ii) Outcome measures

Primary outcomes:
1. Prevalence of anemia
2. Education achievement assessed by a battery of tests of reading, writing and arithmetic

Secondary outcomes:
3. Prevalence of malaria parasitemia
4. Concentration as assessed by classroom-based tests of sustained attention
5. Classroom behavior as assessed by teacher ratings of children’s inattentive and hyperactive-impulsive behaviors.
6. School attendance as assessed by class attendance registers
7. Examination results as assessed by government examination scores

iii) Study sites

The study will take place in rural primary schools in Kwale district, a hot and relatively dry area on the Kenyan coast. Continuous precipitation supports intense year-round transmission, with two seasonal peaks in malaria cases reflecting the bimodal rainfall pattern, with the heaviest rainfall typically occurring between April and June, with a smaller peak in October and November each year. Most malaria is caused by Plasmodium falciparum. A recent survey among 25 schools in 2008 found that the prevalence of malaria infection among schoolchildren in Kwale district was 9% (ranging from 1-28% by school), and 20% (3-37% by school) of children are anaemic (Brooker and Mwandawiro, unpublished data). Helminth infections are also common with 38% of schoolchildren estimated to be infected with hookworm and 41% infected with Schistosoma haematobium.

Kwale district also has some of the poorest educational indicators in the country, with the district having the worst KCPE examination scores for the last three years running.

iv) Study populations

Children enrolled in participating schools will be assessed for the following eligibility criteria:

1. Inclusion criteria
   a. Pupil enrolled at participating schools in standards 1-5
   b. Provision of informed consent from parent or guardian
   c. Provision of assent by student

2. Exclusion criteria
   a. Pupils unwilling to participate in the study
   b. Known allergy or history of adverse reaction to study medications
   c. Known or suspected sickle-cell trait. These children will be referred to testing and/or clinical management as per national guidelines

v) Sample size determination

Power analysis was adjusted for clustering (Hayes & Bennett, 1999) and focused on two main outcomes of interest: the percentage of children who are anaemic (hemoglobin <110 g/L), and education achievement assessed by a battery of tests of reading, writing and arithmetic.

For anemia, assuming a baseline prevalence of 20% (as found in the 2008 school surveys in Kwale), an intraclass correlation of between 0.025 and 50 children sampled per school, a sample size of 21 schools with a total of 1,050 children of all ages in each arm was estimated to provide 80% power to detect a 25% reduction in anemia in the intervention group compared to placebo at 5% level of significance. This equates to 84 schools and 4,200 children.

For educational achievement tests, an overall sample size of 100 schools with 50 children per school (5,000 children overall) is sufficient to detect an effect size of 0.2 standard deviation (SD) assuming an intra-class correlation of 0.2 (ICC varied from 0.1 to 0.2 with mathematics and literacy tests in Class 2 in 210 schools in Western Kenya; ICC is expected to be lower in Class 1) and a correlation between baseline and final test scores of 0.7. This sample size is sufficient to detect an effect size of 0.15 SD for concentration tests, which have a lower intra-class correlation (0.07 in the previous study in Bondo).

vi) Randomization and treatment assignment and allocation

Schools will be randomly assigned to one of the four intervention groups using a pre-defined stratified randomization procedure. A computer generated randomization list will be created by a member of the project who will not be directly involved in the conduct of the study. Sealed copies of the original randomization lists and documentation of the procedure used to generate the lists will be stored in KEMRI offices in Nairobi. Prior to the onset of the study, sealed copies of the randomization lists will be distributed to the member of the study team responsible for treatment allocation.
Schools will be stratified into five groups according to school examination performance in previous years, to account for differences in school quality and socio-economic environment. Five schools will be randomly selected from each school-performance stratum, and within each stratum schools were randomly allocated to 1 of 5 coded drug groups using block randomization according to the randomization listing.

vii) Study interventions
In this study, two interventions will be provided: i) intermittent screening and treatment (IST) for malaria and ii) a program of training for primary school teachers to improve literacy instruction.

The malaria prevention strategy will involve all children being screened using rapid diagnostic tests (RDTs) for malaria once a term (thrice yearly). Children (with or without malaria symptoms) found to be RDT-positive will be treated with artemisinin-based combination therapy (ACT). Screening and treatment will be administered by district health workers once a school term, observed by the evaluation research team.

An education intervention will be conducted in half of the schools receiving IST and half of the control schools. The intervention is designed to improved early grade literacy instruction. Recent evidence (Snow et al., 1998) suggests that relatively simple steps can be taken by teachers in order to improve the development of children’s literacy in the early grades. It is particularly important to develop students’ oral language skills (e.g., phonological awareness & vocabulary) and to teach the relationship between letters and sounds in a systematic and explicit fashion. Such instructional techniques are encouraged in the current Kenyan curriculum but teachers face many challenges in implementing them systematically and effectively. The aim of the instructional intervention will be to support teachers in implementing these teaching methods. Specific interventions will be design based on further consultation with all stakeholders and ongoing class observations in Kwale but may include training on (i) how to monitor students’ progress in large classes (ii) developing and using instructional materials for reading (iii) lesson planning for explicit teaching of letter-sound relationships (iv) instructional techniques for large classes.

viii) Survey investigations
Survey tools and procedures have been used previously to estimate the health and educational impact of IPT in Kenyan schoolchildren (Clarke et al., 2008). These standard tools and operating procedures have been adapted based on previous collective experience. These are detailed below and summarized in Table 2.

| Table 2. Outcome measurements |
|------------------------------|
| Outcome                      | Baseline | Follow-up 1 | Follow-up 2 |
| Consent                      |          |             |             |
| Hb concentration             |          |             |             |
| Malaria parasitaemia         |          |             |             |
| Child literacy and numeracy  |          |             |             |
| School attendance            |          |             |             |
| Behavioural assessments      |          |             |             |
| Socio-economic and educational covariates | | | |
| Soil-transmitted helminths   |          |             |             |
| Urinary schistosomiasis      |          |             |             |

Seeking consent: Selected schools will be visited one month prior to the survey date to have the purpose of the survey explained to the head teacher and school committee, and informed parental consent will be sought from the parents/guardians of children. See section 11. Parents of included children will be asked a series of questions including known parental education, known reactions of their children to anti-malarials, and location of household (Appendix 2). This information will used to (i) help trace children absent from school during follow-up and (ii) control for potentially confounding variables in the data analysis.

Survey procedures: Seven staff travelling in a single vehicle will visit each school: one supervisor; three laboratory technicians; one laboratory assistant; one nurse; plus one driver. An initial meeting will be held with the head teacher. In order to minimize disruption, one class will be selected at a time. Two education testers will assess cognitive function and educational achievement in the week before the arrival of the health team.

A series of questions will be asked of each randomly selected participating child including: age, fever on the day of the survey, basic household assets indicators, source of potable water in the homestead, use of mosquito nets treated with insecticide (Appendix 3). This information will used to control for potentially confounding variables in the data analysis.

On the day of enrollment to the study, children will have their height measured to the nearest 0.1 cm using a portable fixed base stadiometer and weight measured to the nearest 0.1 kg using an electronic balance.

No assessment of malaria parasitaemia and anemia will be made at baseline. However, to measure success of the randomization, children from classes 6 and 7, not enrolled in the study, will be asked to provide a finger-prick blood sample for the preparation of a thick and thin blood smear for malaria investigation. The same finger prick sample will be used at the point of survey to record hemoglobin concentrations using a portable spectrophotometer.

All enrolled children in classes 1 to 5 will be asked to provide a finger-prick blood sample at follow-up to assess malaria parasitaemia and anemia.
For those children with a reported fever or a history of fever in the last 48 hours, a drop of blood will be used to perform a rapid malaria test (OptiMal). Any child with a positive test and symptoms will be treated using arteether-lumefantrine (Co-artem) on the day of the survey according to national guidelines or referred to the nearest health facility if necessary. Transportation costs will be provided and an agreement will be reached with facilities to waive appropriate drug costs. Children identified as severely anaemic (hemoglobin levels < 8 g/dL) will receive ferrous sulphate according to national guidelines.

As part of a national school-based deworming, all schools in Kwale district would have received mass treatment for STH infection using albendazole [400mg]. Therefore, no anthelmintic treatment will be provided in the present study. During the final follow-up pots for stool samples will be distributed to all selected children who will be asked to return the following day with a sample. Children will also be asked to provide a urine sample. These results will be used to assess the need for further anthelmintic treatment, in accordance with national guidelines: mass treatment for STH infection using albendazole [400mg] with a sample. Children will also be asked to provide a urine sample. These results will be used to assess the need for further anthelmintic treatment. In schools where prevalence exceeds 50%; mass treatment for S. haematobium [40 mg/kg] in schools where prevalence exceeds 50%; in remaining schools, only those found to be infected with S. haematobium will be treated.

ix) Education and cost-effectiveness assessments

Pre- and post-intervention education assessments will be performed in each school. This will involve a number of visits per year to each school. The first visit will occur one week prior to the biomedical assessments and will commence with classroom tests of attention for 30-60 minutes in standard 1 and individual assessments of pre-literacy and pre-numeracy skills. A team of 4 people can assess 60 children (2 classes) per day. With two survey teams, 10 schools can be surveyed per week and the pre-intervention surveys will be completed in all schools in 10-12 weeks. In the following term, the teams will return to conduct spot checks of attendance and to conduct classroom observations of pupil behavior and teaching methods. Two people can complete a school in one day and the assessment will take 5 weeks to complete. In the final term, the teams will return to conduct individual cognitive tests and detailed tests of literacy development. These tests will be on an individual basis and will take 4 testers 2 days to complete one school, taking around 15-20 weeks to complete.

Assessments will measure the foundational skills for literacy acquisition: specifically, letter knowledge, phonological awareness, print concepts, individual word reading, passage reading, and spelling. These foundational skills are recognized in the reading literature to be predictive of later reading acquisition in alphabetic languages. Furthermore, they are useful assessments because they are informative about a student’s literacy knowledge and avoid floor effects. The assessments do not duplicate current Moe assessments. Instead, the current study will assess the literacy skills that are needed by a student if they are to meet the MoE goal that “the learners should acquire reading skills to enable them to read and understand instructions, to read for information, and for pleasure (p. 55, Primary English Syllabus, 2002).” The method used to assess educational performance is appropriate for the local situation. People from the local community will be hired to serve as educational assessors. Since the assessments are administered individually, assessors will be trained to ensure children feel comfortable and can clarify the directions in the mother tongue. In addition, brief assessments are used in consideration of young children’s attention spans.

The design of both literacy intervention and the assessment methods is the result of discussions with Ministry staff and other partners, including the Director of Primary Education, Kenya Ministry of Education, and Aga Khan Foundation and African Population and Health Research Centre (APHRC), who are developing literacy interventions for implementation in Coast Province.

The following educational assessments will be undertaken.

School attendance: Data on attendance over the year will be obtained from class attendance registers kept by teachers and which are completed daily as a routine. The registration system will be modified slightly to distinguish between absences due to illness (recorded as S) and those due to other causes (e.g. funerals, travel, home duties, recorded as O). Recording of absenteeism using the modified method will start three months prior to the intervention to establish the procedure in schools. Spot checks will be carried out for quality control. This method has worked successfully in other school health research projects in Kenya (Miguel & Kremer, 2003), although in invariably subject to reporting bias. Class attendance records will be collected at the end of each term for data entry.

School performance: In order to assess whether any improvements in attendance and attention result in increased learning at school, a test of school performance will be administered before treatment and at several subsequent points during the trial. School performance will be evaluated amongst all children in the study cohort, beginning in standard 1. We will assess all subjects but will focus particularly on the development of children’s literacy and numeracy (Appendix 4 and 5). Recent evidence suggests that the Early Grade Reading Assessment (EGRA) is a cost-effective and simple means to assess children’s literacy skills in the early grades (Jukes, Vagh, & Kim, 2006; RTI, 2008). Similar evaluation tools are available for early numeracy.

Assessing mechanisms for the effect on improved school performance: The impact of disease prevention on educational achievement happens through a number of different routes – more time spent in class, more time spent on-task whilst in class and improved cognitive abilities devoted to the task. The battery of behavioral assessments will be extended to capture full range of potential effects of the intervention (Appendix 6). A particular focus will be given to executive function tasks, such as sustained attention. These have been shown to be sensitive to the impact of malaria and anaemia and are important for educational achievement in the early grades. Teams will also spend time in classrooms observing teacher and pupil behavior to assess how this changes in response to malaria intervention and teacher training (Jukes et al., 2006).
Tests will be conducted on the same day as, and immediately before, assessments of parasitaemia and anemia. This will allow an analysis of the covariance between these biological indicators and ability to concentrate.

**Educational covariates:** Recent analyses of large school-based cluster controlled trials (Raudenbush et al., 2007) demonstrates that power can be increased considerably through the assessment of an extensive range of covariates, including teacher and school characteristics and classroom behavior. These will be assessed in the current study as part of the behavioral and educational assessment battery. We will assess parental education and support for their children’s education, teacher’s levels of training, provision of textbooks, desks and other materials in the schools, and other socioeconomic covariates (Appendix 7). A subset of families will be selected to conduct further interviews about how literacy development is supported in the home.

**Classroom Visits:**

The evaluation is interested in differences between teachers’ instructional behaviors that lead to better reading outcomes. With the teacher’s permission, we will video their classroom instruction while simultaneously observing. Each teacher will be observed several times with two instruments. The Stalling (Stallings, 1980) instrument codes the activities engaged in and materials used at multiple time points within one class period. The second instrument, the CLASSIC (Scanlon et al., 2003), assesses specific methods for literacy instruction. Following the lesson, the observer will meet with the teacher for about 30 minutes for a structured interview. The observations, videos, and interviews will support a more detailed analysis of how teachers’ behaviors differ and help our understanding of the ways teachers can influence their pupils’ reading acquisition.

**Cost benefit and effectiveness analysis:** The evaluation will also examine the costs, cost-benefits and cost-effectiveness of IST in improving educational and health outcomes. The costs of IST will be assessed from both a provider’s and societal perspective. Both financial and opportunity costs will be evaluated using standardized methodologies (Drummond et al., 2005). In addition to estimating the rate of return to education, cost-benefit analysis will incorporate improved cognition and learning into the benefit streams (Jimenez & Patrinos, 2008). A comparison of and benefits of other education interventions in Kenya (e.g. Miguel & Kremer, 2004; Glewwe et al., 2004; Glewwe & Kremer, 2006) will also be undertaken. Cost per case of anemia will also be assessed.

**Process evaluation:** This will aim to (i) investigate community acceptability of malaria intermittent screening and treatment; and (ii) document factors external to the intervention which might impact upon both its implementation and its effectiveness. Such an evaluation will help the interpretation of results and help inform future large-scale implementation of the intervention.

First, a modified stakeholder analysis approach will be adopted to identify and assess the importance of key people, or groups of people who are likely to affect the implementation and longer-term sustainability of the program (Steckler & Linnan, 2004; Varvasovszky & Brugha, 2000). Key stakeholders are likely to include: teachers, parents, children, community leaders, local health workers and education officers as well as individuals at provincial and central levels in the Ministries of Education and Health. Stakeholders from both intervention and control schools will be included in order to obtain views on the intervention, but also the acceptability of not immediately receiving the intervention. An assessment will be made of their importance to the success and sustainability of the program and data on their views about the program (e.g., expectations of the intervention, experiences of the intervention, acceptability of the approach, value to individuals & communities, impact on workload) will be collected through a series of focus group discussions as well as semi-structured interviews with people identified as key informants (Bernard, 2006). Discussions and interviews will be transcribed and translated, and content analysis using Nvivo 8 (QSR International, Melbourne, Australia) will be undertaken to identify themes based on people’s experience and involvement in the intervention.

Second, an analysis will be undertaken of the structural, organizational and management factors that enhance or constrain effective implementation of this and other school-based screening and treatment programs, for example, deworming and vitamin A, by staff from the Ministries of Health and Education. In addition to identifying and mapping these stakeholders through the stakeholder analysis, interviews will be conducted with purposefully selected key stakeholders in order to assess the organization and managerial capacities of the government at national and local levels (Jones et al., 2008). These data will be analyzed and interpreted iteratively based on implementation and organizational management theories (Damschroder et al. 2009) and the developed stakeholder analysis framework.

**Laboratory procedures**

Thick and thin blood smears will be stained with 2% Giemsa for 30 minutes and read by experienced laboratory technicians. Parasite densities will be calculated by counting the number of asexual parasites per 200 leukocytes (or per 500 leukocytes, if the count is <10 asexual parasites/200 leukocytes), assuming a leukocyte count of 8000/µl. A blood smear will be considered negative when the examination of 200 high power fields does not reveal asexual parasites. Thin smears will also be made for counting high parasitaemias. For quality control, all slides will be read by a second microscopist and a third reviewer will settle any discrepant readings.

Hemoglobin levels will be measured using a portable HemoCue photometer (HemoCue, Angelholm, Sweden).

Stool examinations will be conducted to determine the prevalence and intensity of intestinal nematodes, using the Kato-Katz method. Urine examinations will also be conducted to determine the prevalence and intensity of *Schistosoma haematobium*, using the urine filtration method.

**Sponsor**

The sponsor of the study will be the London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.
KEMRI, though CMRG-C, Kilifi, will take on the role of database management for active and passive case detection and monitoring of laboratory and field studies. However, SAEs will be reported to the Data Safety Monitoring Board (see below).

**xii) Data Safety Monitoring Board (DSMB)**

An independent committee consisting of experts in malaria, epidemiology, statistics and other appropriate disciplines has been appointed to oversee ethical and safety aspects of the study conduct. A quorum of 3 members is required at scheduled meetings.

The role of the DSMB includes the review of the implementation and progress of the study. It provides initial, regular, and closing advice on safety-related issues to the study sponsor. Its advice is based on the interpretation of study data with reference to the study protocol. The DSMB may, if deemed necessary, convene a meeting with, or request further information from the Principal Investigators and Local Safety Monitors at any stage of the study. The DSMB is empowered to suspend the enrollment to the trial and/or drug treatment on the trial pending review of potential safety issues arising in this trial or other relevant trials of the same drug product. The process will be described in study-specific SOPs. The DSMB will be informed of:

- All SAEs.
- All withdrawals of study subjects by the Principal Investigator or the parent(s)/guardian(s) of a subject due to adverse events.
- New information that may affect adversely the safety of the subjects or the conduct of the study.
- All subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review.
- All subsequent protocol modifications (for information).

The final analysis will be conducted by the investigators, but the analysis plan will be discussed with and approved by the DSMB before it is implemented.

**xiii) Local Safety Monitor (LSM)**

The overall role of the Local Safety Monitors (LSM), who are experienced clinicians based in-country and based in Kilifi or Nairobi, will be to support the clinical investigators and to act as a link between the investigators and the DSMB. The LSM's role will include:

- Acting as the study volunteer's advocate.
- Promptly communicating relevant safety information to the DSMB.
- Providing advice to the investigators on whether a set of clinical circumstances in a study warrants formal notification to the DSMB.
- Conduct a site visit to investigate every report of a SAE
- Unblinding a subject if deemed necessary to allow for adequate treatment.
- Liaising closely with the chair of the DSMB throughout the course of the trial.

The relevant LSM will be informed by the investigator on an 'as received' basis of:

- All SAEs.
- All withdrawals of study subjects by the Principal Investigator or the parent(s)/guardian(s) of a subject due to adverse events.

**xiv) Adverse event monitoring**

An adverse event (AE) is defined as "any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment" (ICH Guidelines E2A). An adverse event can further be broadly defined as any untoward deviation from baseline health which includes:

- Worsening of conditions present at the onset of the study.
- Deterioration due to the primary disease.
- Intercurrent illness.
- Events related or possibly related to concomitant medications.

A serious adverse event (SAE) is defined as an experience that results in any of the following outcomes:

- Death during the period of study follow-up.
- Life-threatening experience (one that puts a participant at immediate risk of death at the time of the event).
- Inpatient hospitalization during the period of study follow-up.
- Persistent or significant disability or incapacity.
- Specific medical or surgical intervention to prevent one of the other serious outcomes listed in the definition.

*Identification of adverse events*

On days 2 and 3 of treatment, study clinicians will assess children according to a standardized clinical record form (Appendix 8). Children absent from school on these days will be traced at home using information collected from parents during the consenting procedure.

Adverse events will be monitored for a further 28 days using a passive surveillance system in schools and local health centers. Travel costs will be reimbursed and treatment charges waived. Any new event, or an event present at baseline that
is increasing in severity, will be considered an adverse event. Adverse events will be monitored until the event has cured or stabilized.

**Reporting of adverse events**

For each possible adverse event identified and graded as moderate, severe or life threatening, an adverse event report form will be completed (Appendix 9). The following information will be recorded for all adverse experiences that are reported:

- Description of event
- Date of event onset
- Date event reported
- Maximum severity of the event
- Maximum suspected relationship of the event to study medication
- Is the event serious?
- Initials of the person reporting the event
- Was the event episodic or intermittent in nature?
- Outcome
- Date event resolved

Grading of events will be based on standard guidelines (Appendix 10).

**Reporting of serious adverse events**

Guidelines for reporting of serious adverse events provided by the KEMRI, the London School of Hygiene & Tropical Medicine, and the data and safety monitoring board (DSMB) will be followed.

**xv) Quality control**

All members of the study team will be trained in the study objectives, methods of effective communication with study participants, and collection of high quality data. Study members will receive additional training specific to the tasks they will perform within the study including interviewing techniques, and clinical and laboratory measurements. A random sample of stool, urine and blood samples will be re-read by experienced technicians and any disparities corrected.

9. Data management

**Data entry and storage**

All questionnaires will be transferred to Kilifi for review, data entry, and storage. Data will be entered by two independent clerks, will be verified for data entry errors, and corrected from the original questionnaire using customized software (Microsoft Visual FoxPro® 6.0) and verified for accuracy. Study records will be stored securely in KEMRI facilities.

**Data analysis**

All analyses will be on the basis of intention-to-treat. To assess the success of randomization baseline characteristics between the four randomization groups will be compared. To assess the impact of the interventions, methods appropriate for cluster-randomized trials will be used (Hayes & Bennett, 1999). The prevalence, or mean, in each school will be calculated and the unadjusted risk ratio (RR), or mean difference (intervention-control), estimated in each stratum. An overall estimate of the effect of IST will be obtained by taking a weighted average of the stratum-specific estimates, the weights proportional to the number of schools per stratum, and 95% confidence intervals will be adjusted for observed between-school variance. Formal hypothesis testing will be undertaken using stratified unpaired t-tests. The impact of each intervention will be estimated for education outcomes and health outcomes in separate multiple regression models. An interaction term will be included to identify any synergistic effects between the two interventions. Statistical analysis will be carried out using STATA® software, version 10.0. (Stata Corporation, Texas, USA).

10. Time Frame

| Year | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 2008 |     |     |     |     |     |     |     |     |     |     |     |     |
|      |     |     |     |     |     |     |     |     |     |     |     |     |
| 2009 |     |     |     |     |     |     |     |     |     |     |     |     |
|      |     |     |     |     |     |     |     |     |     |     |     |     |
|      |     |     |     |     |     |     |     |     |     |     |     |     |
| IST  |     |     |     |     |     |     |     |     |     |     |     |     |
| Assessment of class behavior | | | | | | | | | | | | |
| 2010 |     |     |     |     |     |     |     |     |     |     |     |     |
|      |     |     |     |     |     |     |     |     |     |     |     |     |
|      |     |     |     |     |     |     |     |     |     |     |     |     |
| IST  |     |     |     |     |     |     |     |     |     |     |     |     |
| Assessment of class behavior | | | | | | | | | | | | |
First follow-up health and education surveys

11. Ethical considerations

Informed consent process
Prior to the onset of the study, parent-teacher association meetings will be held with the parents/guardians of children enrolled in standards 1-5 to describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Information sheets (Appendix 11) will be provided to the parents or guardians for their review. For those parents who do not attend these meetings, follow-up will be made through community leaders and household visits.

The parents or guardians will be asked to sign consent for their child (if aged under 18 years) to participate in the research study (Appendix 11). If the child is aged 18 years or over, is married or is a mother (so-called emancipated minor by Kenyan law), they will be asked to provide consent themselves. If a parent, guardian or older child is unable to read or write, his/her fingerprint will be used in substitute for a signature, and a signature from a witness to the informed consent discussion will be obtained. Parents and guardians will have the chance to ask questions and will be informed that participation of their child(ren) in the study is completely voluntary and that they may withdraw from the study at any time.

Information about all children, including age, gender, and any history of known allergies or adverse reactions to study medications, will be obtained from parents/guardians and captured on an initial screening form (Appendix 2). Details about the location of the students’ homes will also be obtained from the parent/guardians to facilitate tracing in the event of absence from school on subsequent follow-up visits. A record will be made of those children for whom consent is provided and will be cross-checked against school registers.

Written consent to participate in the stakeholder interviews and focus groups discussions will be sought.

Verbal assent to participate in the study will also be obtained from the child at the time of screening (Appendix 11).

Training for those involved in administering consent
All fieldworkers will undergo training prior to both studies. Training will educate fieldworkers on the purpose of the study, the importance of consent and how to administer both the consent forms and questionnaires. While in the field, fieldworkers will have continuous contact through the use of a mobile phone with the team leaders in case of any queries.

Community engagement
Prior to the onset of the study, meetings will also be held with officials from the District Education Office, the District Health Management Team and District Commissioner’s office to sensitize them about the study and plans for recruitment and follow-up. Similar meeting will also be held with official at the national level in Nairobi.

Upon completion of the study, a two page ‘Research Brief’ will be developed, similar to that developed for the Bondo study. In addition, a one-day meeting with head teachers of participating schools, district health and education staff will be held, where the results of the study will be presented and discussed. Head teachers will be asked to distribute the Research Brief to interested parents. At the national level, results will be disseminated primarily to the Division of Malaria Control (Ministry of Public Health and Sanitation) and the School Health and Nutrition Programme (Ministry of Education). Finally, a half-day workshop will be convened in Nairobi by the World Bank where the implications of the results will be discussed in light of current school health plans.

Ethical approval
Ethical approval for this study will be obtained from KEMRI National Ethical Committee and the London School of Hygiene and Tropical Medicine before commencement of the study.

Benefits
This study has been designed to address several areas of major public health and educational significance for Kenyan schoolchildren. If we are able to show that malaria treatment improves educational outcomes, millions of African schoolchildren living in malaria endemic regions may benefit.

Children randomized to treatment intervention arms will benefit from free medical treatment for asymptomatic malaria infections. Rapid malaria tests will be performed for those who have a history of fever or raised temperature so that those with malaria parasites can immediately receive treatment, or referred to the nearest health facility, instead of waiting for the slides to be read.

Risks
Parents/guardians and children will be informed of all potential risks.

This study involves collection of finger-prick blood samples which may lead to minor temporary discomfort or pain for children. Precautions will be taken to avoid bleeding by immediate application of sterilized cotton wool and pressure at the prick site. Risks of infection will be minimized by using disposable lancets, one for each child to avoid cross contamination/transmission of infectious agents. Stool and urine sample collection may be embarrassing for the children, but this discomfort will be minimized by guaranteeing children’s privacy during stool collection.

The study involves specific risks from the from the artemisinin-based combination therapy (ACT) drugs. ACTs are remarkably well tolerated in humans, with no serious adverse events or significant toxicity reported.
Confidentiality
Participants, parents and guardians will be informed that participation in a research study may involve a loss of privacy. All records will be kept as confidential as possible. Participants will be identified primarily by their study number and patient names will not be entered into the computerized database. No individual identities will be used in any reports or publications resulting from the study.

12. Expected Application of Results
The results will be disseminated primarily to the Division of Malaria Control (Ministry of Public Health and Sanitation) and the School Health and Nutrition Programme (Ministry of Education), as well as to the District Health Management Team and District Education Office, and other interested stakeholders. This study form part of the evidence-base required by the government of Kenya to inform the decision as to the appropriate malaria control strategy in schools. For example, it will be important to know whether both health and education intervention is required to improve educational outcomes. The evidence may also be useful to other African countries thinking of developing similar interventions and to national and international organizations that may be willing to fund such interventions at a national level. It is also anticipated that the results will be presented at appropriate national and international scientific meetings and several papers will be written and submitted to peer-reviewed scientific journals for publication.

13. References
Adams, M. J. (1990). Beginning to read: Thinking and learning about print. Cambridge, MA: MIT Press.
August, D. L, & Shanahan, T. (Eds.) (2006). Developing literacy in second-language learners: Report of the National Literacy Panel on Language-Minority Children and Youth. Mahwah, NJ: Lawrence Erlbaum Associates.
Bernard HR (2006) Research methods in anthropology: qualitative and quantitative approaches. Oxford, UK: AltaMira Press.
Blair, C., & Razza, R. P. (2007). Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. Child Development, 78(2), 647-663.
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? Parasitology Today, 16(5), 183-186.
Clarke, S. E., Brooker, S., Njagi, J. K., Njau, E., Estambale, B., Muchiri, E., et al. (2004). Malaria morbidity among school children living in two areas of contrasting transmission in western Kenya. Am J Trop Med Hyg, 71(6), 732-738.
Clarke SE, Jukes MCH, Njagi K, Khasakhalha L, Cundill B, Otido J, Crodder C, Estambale B, Brooker S: Health and educational impact of school-based intermittent preventive treatment in Kenya: a placebo cluster-randomised controlled trial. Lancet 372, 127-138.
Commeyras, M. & Inyega H. N. (2007). An integrative review of teaching reading in Kenyan primary schools Reading Research Quarterly, 42, 258-281.
Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC (2009). Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implementation Science, 4:50.
Denis, M. B., Davis, T. M., Hewitt, S., Incardona, S., Nimol, K., Fandeur, T., et al. (2002). Efficacy and safety of dihydroartemisinin-piperaquine (Artekina) in Cambodian children and adults with uncomplicated falciparum malaria. Clin Infect Dis, 35(12), 1469-1476.
Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL: Methods for the economic evaluation of health care programmes. Third edition. Oxford: Oxford University Press; 2005.
Duflo E & Kremer M. Use of Randomization in the Evaluation of Development Effectiveness. In Evaluating Development Effectiveness (World Bank Series on Evaluation and Development, Vol 7). Edited by Osvaldo Feinstein, Gregory K. Ingram and George K. Pitman. New Brunswick, NJ: Transaction Publishers; 2004: 205-232.
Fernando, D., Wickremasinghe, R., Mendis, K. N., & Wickremasinghe, A. R. (2003a). Cognitive performance at school entry of children living in malaria-endemic areas of Sri Lanka. Transactions of the Royal Society of Tropical Medicine and Hygiene, 97(2), 161-165.
Fernando, S. D., Gunawardena, D. M., Bandara, M., De Silva, D., Carter, R., Mendis, K. N., et al. (2003b). The impact of repeated malaria attacks on the school performance of children. American Journal of Tropical Medicine and Hygiene, 69(6), 582-588.
Geerligs, P. D., Brabin, B. J., & Eggelte, T. A. (2003). Analysis of the effects of malaria chemoprophylaxis in children on haematological responses, morbidity and mortality. Bull World Health Organ, 81(3), 205-216.
Glewwe P, Kremer M, Moulin S, Zitzewitz E. Retrospective vs. prospective analyses of school inputs: The case of flip charts in Kenya. “Economics and Policy of Development” Volume 20, 251–268.
Glewwe P, Kremer M. Schools, Teachers, and Education Outcomes in Developing Countries," in E.A. Hanushek and F. Welch, eds., Handbook of the Economics of Education, Volume 2. Elsevier, 2006.
Hayes RJ, Bennett S (1999). Simple sample size calculations for cluster-randomized trials. Int J Epidemiol 28: 319–326
Holding, P. A., & Snow, R. W. (2001). Impact of Plasmodium falciparum malaria on performance and learning: review of the evidence. Am J Trop Med Hyg, 64(1-2 Suppl), 68-75.
Jimenez E, Patrinos HA. Can Cost-Benefit Analysis Guide Education Policy in Developing Countries? Policy Research Working Paper 4568. Washington DC: World Bank, 2008
Jimerson, S., Egeland, B., & Teo, A. (1999). A longitudinal study of achievement trajectories: Factors associated with change.
Jones C, Abeiku TA, Rapuoda B, Okia M, Cox J (2008). District-based malaria epidemic early warning systems in East Africa: perceptions of acceptability and usefulness among key staff at health facility, district and central levels. Social Science and Medicine, 67(2),292-300.
Jukes, M. C. H., Vagh, S. B., & Kim, Y. S. (2006). Development of Assessments of Reading Ability and Classroom Behavior: World Bank.
Karunajeewa, H., Lim, C., Hung, T. Y., Ilett, K. F., Denis, M. B., Socheat, D., et al. (2004). Safety evaluation of fixed combination piperaquine plus dihydroartemisinin (Artekin) in Cambodian children and adults with malaria. *Br J Clin Pharmacol*, 57(1), 93-99.

Kurtzhals, J. A., Addae, M. M., Akanmori, B. D., Dunyo, S., Koram, K. A., Appawu, M. A., et al. (1999). Anemia caused by asymptomatic *Plasmodium falciparum* infection in semi-immune African schoolchildren. *Trans R Soc Trop Med Hyg*, 93(6), 623-627.

Laloo, D., Oluikoya, P., Oliaro, P. (2006). Malaria in adolescence: burden of disease, consequences and opportunities for intervention. *Lancet Infectious diseases*, 6, 780-793.

Leighton, C. & Foster, R (1993). *Economic impacts of malaria in Kenya and Nigeria*. Major Applied Research Paper no 6, HFS project, Abt Associates, Bethesda.

Miguel, E., & Kremer, M. (2004). Worms: Identifying impacts on education and health in the presence of treatment externalities. *Econometrica*, 72(1), 159-217.

Ministry of Education Science and Technology (MOEST) (2001). *Teaching and learning English in the primary classroom: English module*. Nairobi: Jomo Kenyatta Foundation.

Muthwii, M.J. (2004). Language planning and literacy in Kenya: Living with unresolved paradoxes. *Current Issues in Language Planning*, 5, 34—50.

National Institute of Child Health and Human Development (NICHD) (2001). *Report of the National Reading Panel. Teaching children to read: An evidence-based assessment of the scientific research literature on reading and its implications for reading instruction* (NIH Publication No. 00-4769). Washington, DC: U.S. Government Printing Office.

Nzomo, J., Karuki, M., & Guantai, L. (2001). *The quality of primary education in Kenya: Some suggestions based on a survey of schools*. Paris: International Institute for Educational Planning/United Nations Educational, Scientific and Cultural Organization.

Olliaro P, Nevill C, LeBras J, Ringwald P, Mussano P, Garner P, Brausseur P (1996). Systematic review of amodiaquine treatment in uncomplicated malaria. *Lancet* 348:1196-1201.

Phillips-Howard PA, West LJ (1990). Serious adverse drug reactions to pyrimethamine-sulphadoxine, pyrimethamine-dapsone and to amodiaquine in Britain. *Journal of the Royal Society of Medicine* 83(2):82-85.

Raudenbush, S. W., Martinez, A., & Spybrook, J. (2007). Strategies for improving precision in group-randomized experiments. *Educational Evaluation and Policy Analysis*, 29(1), 5-29.

Scanlon DM, Gelzheiser L, Fanuele D, Sweeney J & Newcomer L (2003). Classroom Language Arts Systematic Sampling and Instructional Coding (CLASSIC). Unpublished manuscript, Child Research and Study Center, The University at Albany.

Snow, C. E., Burns, M. S., & Griffin, P. (Eds.). (1998). *Preventing Reading Difficulties in Young Children*. Washington, DC: National Academy Press.

Snow RW, Craig MH, Newton CRJC, Steketee RW (2003). The public health burden of *Plasmodium falciparum* malaria in Africa: Deriving the number. Working Paper No. 11, Disease Control Priorities Project. Bethesda, Maryland: Fogarty International Center, National Institutes of Health.

Stallings J (1980). Allocated academic learning time revisited, or beyond time on task. *Educational Researcher* 9, 11-16.

Taylor WR, White NJ (2004) Antimalarial drug toxicity: A review. *Drug Safety* 27:25–61.

Temperley M, Mueller D, Njagi K, Akhwale W, Clarke SE, Jukes MCH, Estambale BBA & Brooker S (2008) Costs and cost-effectiveness of delivering intermittent preventive treatment for malaria through schools in western Kenya. *Malaria Journal* 7, 196.

Varvasovszky Z, Brugha R (2000): A stakeholder analysis. *Health Policy and Planning*, 15(3):338-345.
14. Budget ($1 = 76.3 Ksh)

| Item | Amount (US$) | Amount (Ksh) |
|------|--------------|--------------|
| a) Personnel salaries and benefits | 259,000 | 19,761,700 |
| b) Patient Costs | 22,500 | 1,716,750 |
| c) Equipment | 32,450 | 2,475,935 |
| d) Supplies | 16,750 | 7,382,025 |
| e) Travel and accommodation | 16,000 | 1,220,800 |
| f) Transportation | 86,450 | 6,596,135 |
| g) Operating expenses | 260,500 | 19,876,150 |
| h) Animals | Not applicable | Not applicable |
| i) Consultancy fees | Not applicable | Not applicable |
| j) Contingency funds | 75,000 | 5,722,500 |
| k) Institutional administrative overheads | Not applicable | Not applicable |
| **Total** | **768,650** | **58,647,995** |

15. Justification of Budget

*Personal salaries and benefits.* This includes salaries and benefits of field coordinators, fieldworkers and technicians.

*Patient costs.* This includes anti-malarials and placebos for all children as well as albendazole, prazquantel, Co-artem and ferrous sulphate, as required.

*Equipment.* This is estimated for the purchase of motorcycles large equipment including microscopes and Hemocue machines.

*Supplies.* This is the estimated cost of all the non-field work supplies required for the study at the KEMRI-Wellcome unit in Nairobi. It includes photocopying, stationary, communication and printing over the survey period. The estimates are based on routine costs charged at the unit.

*Travel and transportation.* During the study preparation an investigator will need to meet with local officials and school head teachers. Travel and accommodation costs for these trips have been factored in here.

The education component of the study involves modifying the way Standard 1 and 2 classroom teachers develop their students’ literacy skills. To do this, the intervention includes an initial residential teacher training over a four-day period followed by ongoing monitoring and support. To ensure that all of the school’s personnel are informed, the Head Teachers and the Senior Teachers will also be invited to the training. This way, they will be available to support the classroom teachers during the implementation of the intervention. The literacy intervention will be implemented in 50 schools involving at least three teachers from each.

The study has a longitudinal design to investigate the interaction of the malaria intervention and the literacy intervention. To understand the effects of the interventions we will measure students’ education achievement at the onset and end of the interventions. Student achievement in 100 schools will be measured. While the surveys are going on, a supervisor, three laboratory technicians, one laboratory technician, one interviewer, one nurse plus one driver will need to travel to the field sites to undertake school surveys. All costs for travel and accommodation have been estimated using standard KEMRI mileage and per diem charges.

*Operating costs.* This includes all costs required to carry out the field studies and include laboratory materials, supplies, reagents and disposables. Training workshops will be organized by ESACIPAC to train all the technicians at the DVBD in Kwale hospitals on parasite microscopy. Also included are laboratory quality control costs.