Comparing approaches for chemoprevention for school-based malaria control in Malawi: an open label, randomized, controlled clinical trial

Alick Sixpence,[a,b] Maclean Vokhiwa,[c] Wangisani Kumalakwaanthu,[b] Nicola J. Pitchford,[d] Karl B. Seydel,[e,f] Laurence S. Magder,[g] Miriam K. Laufer,[h] Don P. Mathanga,[b,i] and Lauren M. Cohee[h,j,*]

[a]Department of Epidemiology and Department of Global Health, Boston University School of Public Health, 715 Albany St, Talbot Building, Boston, MA, 02118, USA
[b]Malaria Alert Centre (MAC), Kamuzu University of Health Sciences (KUHeS), Private Bag 360, Chichiri, Blantyre 3, Malawi
[c]Training & Research Unit of Excellence (TRUE), 1 Kufa Road, Mandala, P.O Box 30538, Chichiri, Blantyre 3, Malawi
[d]School of Psychology, University of Nottingham, Nottingham, UK
[e]Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, East Lansing, MI, 48824, USA
[f]Blantyre Malaria Project, Kamuzu University of Health Sciences, PO Box 32256, Chichiri, Blantyre, Malawi
[g]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA
[h]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
[i]School of Global and Public Health, Kamuzu University of Health Sciences (KUHeS), Private Bag 360, Chichiri, Blantyre 3, Malawi
[j]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, UK

eClinicalMedicine 2024;76: 102832
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102832

Summary

Background School-age children in sub-Saharan Africa suffer an underappreciated burden of malaria which threatens their health and education. To address this problem, we compared the efficacy of two school-based chemoprevention approaches: giving all students intermittent preventive treatment (IPT) or screening and treating only students with detected infections (IST).

Methods In a three-arm, open-label, randomized, controlled trial (NCT05244954) in Malawi, 746 primary school students, aged 5–19 years, were individually randomized within each grade-level to IPT (n = 249), IST with a high-sensitivity rapid diagnostic test (hs-RDT, n = 248), or control (n = 249). At six-week intervals three times within the peak malaria transmission season (February–June 2022) treatment with dihydroartemisinin-piperaquine (DP) was administered to girls <10 years and all boys, and chloroquine to older girls. The primary outcome was *Plasmodium falciparum* (*Pf*) infection detected by PCR 6–8 weeks after the final intervention. Secondary outcomes included anaemia, clinical malaria, and scores on tests of attention, literacy, and math. Analysis was by modified intention-to-treat.

Findings Outcomes analyses included 727 (97%) participants. At the end of the study, prevalence of *Pf* infection was 17% (41/243) in the IPT arm, 24% (58/244) in the IST arm, and 53% (127/240) in the control arm. Compared to controls, IPT and IST reduced the odds of *Pf* infection (IPT adjusted odds ratio [aOR]: 0.18 (95% CI: 0.11, 0.27); p < 0.0001; IST aOR: 0.27 (95% CI: 0.18, 0.40); p < 0.0001). However, only participants receiving IPT had a lower incidence of clinical malaria (0.19 cases per person per six months (95% CI: 0.14, 0.27) vs 0.56 (95% CI: 0.46, 0.68); incidence rate ratio: 0.38 (95% CI: 0.26, 0.55); p < 0.0001)) and prevalence of anaemia (8% [20/243] vs 15% [36/240]; aOR: 0.49 (95% CI: 0.27, 0.91); p = 0.023) compared to controls. Literacy scores were higher in both intervention arms. No between group differences in tests of attention or math or number of serious adverse events were found.

Interpretation Results support implementation of IST with hs-RDTs or IPT for reduction in the prevalence of infection. Based on reductions in clinical malaria, IPT may provide additional benefits warranting further consideration by school-based malaria chemoprevention programs.

Funding Doris Duke Charitable Foundation Clinical Scientist Development Award 2021191, U.S. NIH K24AI114996 & K23AI135076.

*Corresponding author. Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK.
E-mail address: lauren.cohee@lstmed.ac.uk (L.M. Cohee).

Keywords: Malaria; Chemoprevention; School health; Anaemia; Cognition; Education

Research in context

Evidence before this study

In 2020, Cohee et al. published a systematic review and meta-analyses of 13 school-based malaria preventive treatment trials conducted in seven malaria-endemic sub-Saharan African countries. Studies from 1990 to 2018 were included in analyses and demonstrated that preventive treatment decreased *Plasmodium falciparum (Pf)* infection, anaemia, and subsequent clinical malaria. The only study that evaluated a screening and treatment approach, in which only children who test positive for infection are treated, did not decrease *Pf* infection or anaemia. However, screening and treatment is appealing compared to treating all students regardless of infection status as screening and treatment decreases the use of anti-malarial drugs limiting cost and selective pressure on drug resistant parasites. We searched PubMed for publications from the final date of the prior meta-analysis (December 18, 2018) to February 22, 2024, without language restrictions, using the search terms "malaria" AND "school-age" AND "screening" AND "trial" and returned no subsequent randomised trials of the screening and treatment approach.

Added value of this study

Our study is the only randomised trial of school-based malaria chemoprevention to compare the efficacy of both intermittent screening and treatment (IST) and treating all students (intermittent preventive treatment—IPT) to control. By using new higher sensitivity malaria rapid diagnostics as the screening test and a longer acting anti-malarial drug for treatment, the current study also addresses hypothesised reasons for the lack of efficacy in the prior screening and treatment trial. Our findings demonstrate that while both IST and IPT substantially reduced *Pf* infection compared to control, only IPT reduced clinical malaria and anaemia, suggesting that IPT should be the preferred approach for malaria chemoprevention targeting school-age children. Furthermore, students receiving IPT or IST had higher literacy scores compared to their peers in the control arm.

Implications of all the available evidence

In malaria endemic areas across Sub-Saharan Africa, school-age children have a high prevalence of *Pf* infection resulting in episodes of clinical malaria and malaria-related anaemia which contribute to poor health and potentially undermine learning. As of 2023, the World Health Organization's guidelines for malaria recommend the use of intermittent preventive treatment of school-age children (IPTsc) in malaria-endemic settings with moderate to high perennial or seasonal transmission to reduce the disease burden. However, reservations about this approach, including its possible contribution anti-malarial drug resistance, have limited uptake. In contrast to the prior trial, our results suggest IST with more sensitive screening tests, longer acting drugs, and in a higher transmission setting can reduce *Pf* infection. However, the added benefits of IPT (decreased clinical malaria and anaemia) lends additional support for this approach. We provide further evidence for the benefits of reducing malaria in improving not only the health of school-age children but also their learning.

Introduction

Malaria remains a critical global health problem with an estimated 3.3 billion people—half of the world's population—living in areas at risk of malaria transmission.[1] Sub-Saharan Africa accounts for 94% of all cases and deaths associated with malaria. In Malawi, the burden of malaria is high in terms of morbidity, mortality, and socio-economic impacts. Despite the scale-up of malaria interventions including clinical case management and vector control, in many highly endemic countries, progress in malaria control has stalled. Thus, additional interventions are needed to further control the burden of malaria and to move toward the ultimate goal of malaria eradication.

School-age children suffer an underappreciated burden of malaria. Across a range of malaria transmission settings, prevalence of *Plasmodium falciparum (Pf)* infection peaks in school-age children.[2–8] While school-age children are less likely than younger children to experience malaria related mortality and severe malaria disease, malaria is the leading cause of death in 5–14-year-olds in sub-Saharan Africa.[9] Furthermore, infections in this age group frequently result in both uncomplicated clinical malaria disease and chronic *Pf* infections resulting in school absences.[10] Chronic infections are associated with anaemia, malaise, and impaired cognitive function, and often do not prompt treatment seeking and may contribute to decreased attention and learning.[10–12] Of great importance to malaria control, sub-clinical infections in this age group are a major source of *Pf* transmission.[13,14]

School-based preventive treatment, which provides both clearance of current infections and prophylaxis for a period of time determined by the duration of action of the treatment drugs, is an efficacious way to decrease the burden of infection in schoolchildren.[15] An alternative to preventive treatment is to target schoolchildren with sub-clinical infections using an intermittent

screening and treatment (IST) approach, where only students with a positive screening test are treated. IST is an appealing approach because: 1) only students with documented infections are treated and 2) it decreases the use of anti-malarial drugs limiting cost and selective pressure on drug resistant parasites. Observational studies suggest that school-based screening and treatment may be an effective approach to decrease *Pf* infection and anaemia in students as well as reduce community transmission.[13,14] However, to date, only one school-based trial has evaluated the IST approach.[16] This study, a cluster randomized trial in an area of relatively low *Pf* prevalence, used conventional malaria rapid diagnostic tests (RDTs), which detect most infections with at least 200 parasites/μl, to identify infected students once per school term and showed no benefit on *Pf* infection, anaemia, or tests of sustained attention.[16] One explanation for these results is that conventional RDTs fail to detect low density *Pf* infections that represent a higher proportion of infections in low prevalence settings and that these low density infections are associated with adverse outcomes.[17,18]

To our knowledge, no prior studies have directly compared school-based IST and intermittent preventive treatment (IPT) or evaluated the use of new higher sensitivity RDTs (hs-RDT) for IST in schoolchildren. hs-RDTs are ten-fold more sensitive than conventional RDTs facilitating detection of lower density infections.[19,20] Thus, we aimed to compare the impact of IPT and an optimized IST approach using high sensitivity RDTs with a long-acting treatment drug to control in a moderate-high transmission season. We hypothesized that because IPT provides clearance and prophylaxis to all students, it would still offer additional benefits compared to an optimized IST approach. Comparisons will inform future policy on school-based preventive treatment which may be a critical approach to both improve the health and education of schoolchildren and contribute to malaria elimination.

Methods

Study design and setting

This three-arm, individually randomized, open label, clinical trial (ClinicalTrials.gov ID: NCT05244954) was conducted in Nainunje Primary School in Machinga district, Malawi and was approved by the research ethics committees of Kamuzu University of Health Sciences (P.06/21/3410) and the University of Maryland School of Medicine (HCR-HP-00098250-2). The trial took place between February and August 2022 and randomized participants to IPT in which all participants were treated, IST in which only participants with infections detected by high-sensitivity point-of-care screening tests were treated, or control in which participants received standard of care meaning no intervention (details are provided in the Procedures section below). Despite scale up of control interventions, malaria transmission in the area is intense with a seasonal peak between January and May.[21] Government supported malaria control interventions in the study area include access to diagnosis and treatment with lumefantrine artemether as the first-line antimalarial and vector control with piperonyl-butoxide long lasting insecticide treated nets (LLINs) distributed via national campaigns (2018) and routine health centre contacts. Annual incidence of clinical malaria in children less than five years old in the local health centre the year prior to the trial was 1590 cases/1000 people (DHIS2, unpublished). The study site was selected based on significant burden of malaria in the community, total school enrolment sufficient to meet sample size, accessibility, proximity of the local health centre, and willingness of community and school stakeholders to support the study. Sensitization meetings were held with community leaders, teachers, health workers and parents or legal guardians to explain the purpose of the trial.

Participants

Using school registers from all grade levels,[1–8] students were sampled and offered enrolment proportional to the number students in each grade-level (Table S1). Written informed consent was obtained from legal guardians. Assent was sought from participants ten years and older. Students were excluded if they had: current evidence of severe malaria or danger signs, known adverse reaction to the study drugs, history of cardiac problems or fainting, were taking medications known to prolong QT, family history of prolonged QT or unexplained sudden death, or, for girls ten years and older (i.e. those receiving chloroquine), epilepsy or psoriasis.

Randomization and masking

Following enrolment of the target number of participants in each standard (grade-level), participants were randomized with stratification by grade-level to intermittent preventive treatment (IPT), intermittent screening and treatment (IST) and control arms (1:1:1) using a computer-based random number generator. The trial was open label, however laboratory technicians conducting parasite detection (primary outcome) and clinicians conducting passive case detection were blinded to the study arm allocation.

Procedures

Interventions began approximately four weeks after enrolment and were conducted three times at 5–6 week intervals during the peak malaria transmission season. At each intervention all participants in the IPT arm received a three-day course of study drugs, dihydroartemisinin-piperaquine (DP, DuoCotecxin, Holley-Cotec Pharmaceuticals, Beijing, China) or chloroquine (CQ, Lariago, IPCA Laboratories, India). Participants in the IST arm were screened with a high-

sensitivity rapid diagnostic test (hs-RDT, NxTek™ ELIMINATE MALARIA *Pf*, Abbot Diagnostics Korea, Inc.) and treated with study drugs if they tested positive. In the intervention arms, girls less than ten years old and all boys received DP. Because of the risks of artemisinin in the first trimester and the sensitivity around adolescent pregnancy, girls who were likely to have started menses (≥10 years old) were treated with CQ. Both DP and CQ were dosed based on weight (Table S2) once daily for three days. Study drugs were administered at school by study nurses with all doses administered under direct observation. Since the study period coincided with Ramadan, participants observing the fast were either treated at school with parental permission or in the community after sunset. Adverse events were monitored by the study team during treatment and by passive surveillance at the school and local health centre for the duration of the study. An internal safety monitoring committee reviewed adverse events and monitored trial progress.

The control arm did not receive study specific intervention. As part of the school curriculum, all students, regardless of study participation, received standardized malaria education delivered by their classroom teachers. The grade-level specific curriculum includes basics of transmission, preventive measures, and the importance of seeking medical attention upon experiencing symptoms and adhering to prescribed antimalarial medication regimens.

Intervention visits included an interview and finger prick blood sample collection. Final participant assessments took place 6–8 weeks after the last intervention. During enrolment, a standardized questionnaire based on the Malaria Indicator Survey was administered to the household head or primary caregiver to collect data on insecticide treated net ownership and use, highest education level completed by the household head household-level socio-economic status including, asset and livestock ownership, the type of fuel mainly used for cooking, and if the household experienced food insecurity.[22] Using these variables, socio-economic status is reported as an inverse frequency weighted wealth index divided into tertiles.[23] At each intervention visit and the final assessment, the participant interview assessed self-reported bed net use, well-being, fever in the last 48 h, and interval use of anti-malarial treatment. A finger prick blood sample was obtained at each visit. Two 50 µl samples were placed onto Whatmann 3 MM filter paper. At the first intervention and final outcome visits, haemoglobin was also measured (HemoCue 301). In the IST arm at each intervention visit, hs-RDT was performed per manufacture instructions. At the first intervention visit for the IST arm a conventional RDT (SDBioline™ Malaria Ag *Pf*, Abbot Diagnostics) was also performed per manufacture instructions.

The primary outcome was *Pf* infection at the final participant assessment. Briefly, for detection of infection, DNA was extracted from filter papers using methanol[24] and *Pf* 18S ribosomal RNA gene was detected and quantified by qPCR.[25] Secondary outcomes included anaemia, haemoglobin, incidence of clinical malaria, cognitive function (sustained attention, selective attention) and foundational educational skills (basic literacy and math). Anaemia was defined using WHO age and sex specific cut-offs: for children <12 years old, haemoglobin <11.5 g/dl; for all children 12–14 and females 15 and older, haemoglobin <12.0 g/dl; and for males 15 and older, haemoglobin <13.0 g/dl.[26] Cases of clinical malaria were defined as seeking clinical care, having a positive malaria RDT, prescribed antimalarial treatment by a healthcare worker, and occurring more than 28-days after a prior clinical diagnosis. Cases that occurred between the first intervention visit and outcome visit (February–August 2022) were captured by passive case detection at the local health centre and review of the participants' health passport (portable medical record) during the final assessment visit to ensure all clinical malaria diagnoses were documented.

Cognitive function was assessed using measures of sustained and selective attention. For sustained attention, the code transmission test, adapted from TEA-Ch battery and used in prior school-based malaria studies, was conducted by administering the single-digit assessment to participants in grades 3–4 and the double-digit for participants in grades 5–8.[15,27] Selective attention was measured using a tablet-based self-assessment in all grade-levels, which was previously shown to be reliable and valid in Malawian students.[28] Briefly, participants were required to touch coloured circles on the screen as quickly as possible in the presence or absence of distractors. Foundational skills in literacy and math were assessed using onetest—an adaptive, self-administered tablet-based assessment.[29] Participants were oriented to the use of tablets by the study team and talked through a trial of the selective attention test as an orientation. Assessments were administered in groups of 15–20 participants on Android tablets with headphones and proctored by trained assessment teams. Standardization and quality control of the cognitive and educational tests were measured through inter-assessor and test-retest in >10% of all assessments. Measures showed moderate to high degree of reliability between assessors and after 30-day retest with intraclass correlation coefficients ranging from 0.66 to 0.95 (mean = 0.82, 95% CI: 0.62–0.90 ($F(67,67) = 10.38$ $p < 0.001$)), where estimates and 95% confidence intervals are calculated using mean-rating, absolute-agreement, 2-way mixed-effects model.

Statistical analysis

The study sample size (250 participants per study arm, total 750 participants) was based on having 80% power to detect a 40% relative reduction in prevalence (primary outcome) comparing each intervention arm to the

control arm, using one-sided tests with an alpha = 0.025. We assumed an estimated prevalence of *Pf* infection by PCR of 30% in the control arm and allowed for 80% follow-up rate.

Data were analysed by modified intention to treat (mITT) where all randomized individuals for whom outcome measures were available were included in the analysis; only participants who did not attend the outcome visit were not included in the analysis because outcomes data were not available. Baseline characteristics of participants in each arm were calculated using descriptive statistics. For each outcome, formal analyses consisted of pairwise comparisons between each intervention arm and the control arm and between intervention arms.

For the primary outcome, presence of *Pf* infection, groups were compared by logistic regression, controlling for grade-level. Mean of log-transformed total parasite densities were compared at the final visit, including only those with infections (non-zero densities). Formal inference was based on a general linear model with intervention group and grade-level included as categorical predictors. Pair-wise comparisons of the intervention groups was made using Fisher's least significant difference approach. Haemoglobin levels were compared using an ANCOVA model with outcome variable as the haemoglobin level at the final assessment, intervention group as a categorical predictor, and baseline haemoglobin level and grade-level included as covariates. Other variables that were related to haemoglobin levels (e.g. age and sex) were included in the model to reduce the residual variation and thereby increase the power. Prevalence of anaemia was compared by logistic regression, including intervention group, anaemia at baseline and grade-level as categorical variables. Incidence of clinical malaria was compared by Poisson regression using a log-link and offset equal to the log of the number of days a person was followed, controlling for grade-level. Code transmission, selective attention, literacy, and math outcomes are all continuous variables with minimum and maximum values based on the number of possible points on the specific assessment and were compared using general linear models with intervention group included as a categorical predictor and grade-level also included in the model. Pair-wise comparisons of the intervention groups were made using Fisher's least significant difference approach.

Role of the funding source

The funder had no role in the design, data collection, or analysis of the study

Results

Among the 1812 students enrolled in the school, seven hundred and seventy-six students (43%) were assessed for eligibility. Among the 746 participants enrolled and randomized from 1st to 22nd February 2022, 727 participants (97%) were evaluated at the outcome assessment for the primary outcome and were, thus, included in the mITT analysis (Fig. 1, additional details in Figure S1). The 19 participants who did not attend the outcome visit were not different from participants included in the mITT analysis with regard to household-level factors and socioeconomic status (Table S3). Participation in the intervention visits was high with 92% (2055 visits attended/2238 possible visits) participation across study arms. Eighty-two percent (608/746) of participants attended all intervention visits. Treatment compliance was also high: in the IPT arm, among the participants who attended the intervention visits, 98% (691/703) received at least the first dose of treatment, with 86% (594/691) of them successfully completing all three doses (Table S4). In the IST arm, among the participants who tested positive by hs-RDT, 96% (279/292) received at least the first dose of treatment during all intervention visits and, 82% (229/279) of these participants successfully completed all three doses. Two percent of participants in the IPT arm (n = 12) and four percent of participants in the IST arm (n = 13) who attended the visit but did not receive treatment were already taking antimalarial treatment for clinical malaria. At baseline, prevalence of *Pf* infection by PCR for all participants was 52% and participant baseline characteristics were similar across the study arms (Table 1). At the first intervention visit, 49% (114/233) of participants in the IST arm had *Pf* infection detected by hs-RDT, while conventional RDTs detected *Pf* infection in only 39% (92/233).

At the outcome visit, prevalence of *Pf* infection was 53% (127/240), 17% (41/243), 24% (58/244), and in the control, IPT, and IST arms, respectively (Table 2). Compared to control, IPT and IST both significantly reduced the odds of *Pf* infection (aOR: 0.18 (95% CI: 0.11, 0.27), p-value <0.0001; OR: 0.27 (95% CI: 0.18, 0.40), p-value <0.0001, respectively).

Over the study period, there were 244 episodes of uncomplicated clinical malaria recorded in all arms with no cases of severe malaria or mortality. The control arm had a clinical malaria incidence rate of 0.51 per six months (95% CI: 0.42, 0.62), compared to 0.19 (95% CI: 0.14, 0.27) in the IPT arm, resulting in 62% protective efficacy (incidence rate ratio [IRR]: 0.38, 95% CI: 0.26, 0.55, p-value <0.0001, Table 2). The number needed to treat with IPT to avert one case of clinical malaria was 3.9 participants (95% CI: 3.0, 5.6). In the IST arm, the incidence rate of clinical malaria was 0.56 (95% CI: 0.46, 0.68), which was similar to the control arm (IRR: 1.09, 95% CI: 0.83, 1.44, p-value = 0.52). The quantity of commodities (drugs and mRDTs) used in each arm and their costs are included in Table S5.

Participants in the IPT and IST arms had increased haemoglobin levels at the outcome visit compared to the

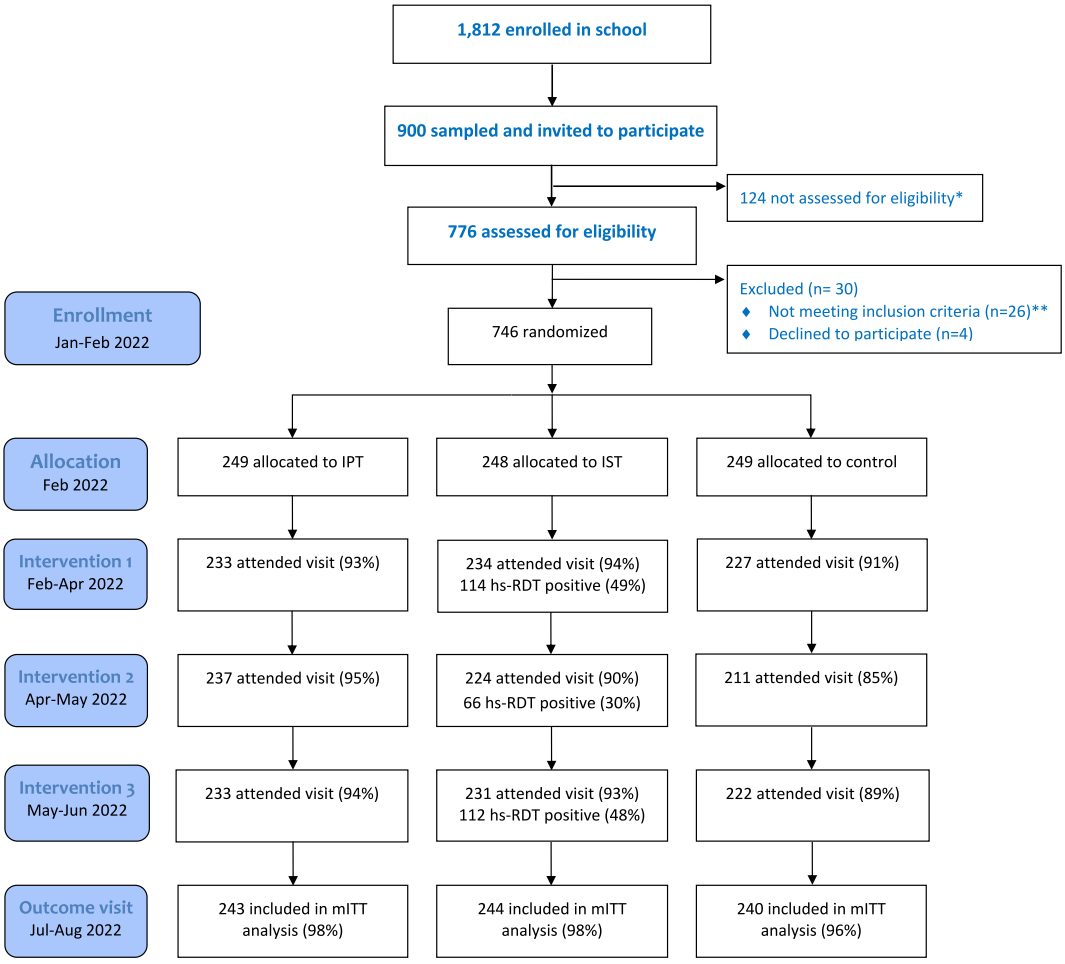

Fig. 1: Trial profile. IPT Intermittent Preventive Treatment; IST Intermittent Screening and Treatment; hs-RDT high-sensitivity malaria rapid diagnostic test; mITT modified Intention to treat. Reasons for not attending intervention visits included absent from school due to travel (n = 2), absent from school for unspecified reasons (n = 164), and declined participation in that visit (n = 1), withdrew consent (n = 14) and no longer attending the study school (n = 11): dropped out, relocated, and transferred (later became withdraws once confirmed). *124 sampled students did not attend the enrolment visit. **26 individuals were excluded based on prespecified criteria: 15 reported heart problems or fainting; 4 reported family history or prolonged QT of sudden unexplained death in a young person; 3 reported both heart problems or fainting and family history or prolonged QT of sudden unexplained death in a young person; 2 girls with epilepsy who also reported heart problems or fainting; 1 reported an antimalaria drug allergy and both heart problems or fainting; and 1 was no longer enrolled at the study school.

control arm (Table 2); after adjustment for pre-intervention haemoglobin, the mean haemoglobin difference was +0.25 g/dl (95% CI: 0.01, 0.48; p = 0.041) for the IPT arm and +0.28 g/dl (95% CI: 0.04, 0.51; p = 0.021) for the IST arm each compared to control. However, only IPT was associated with decreased odds of anaemia with adjusted odds ratio 0.49 (95% CI: 0.27, 0.91; p = 0.023) compared to the control group.

While the trial was not powered for comparisons between the interventions arms, IPT was superior to IST with regard to reducing clinical malaria (Incidence rate ratio: 0.35; 95% CI: 0.24–0.50; p < 0.001). There was some, though not strong, evidence of difference between the groups with regard to *Pf* prevalence and anaemia (aOR 0.66; 95% CI: 0.42–1.02; p = 0.065 and aOR 0.58; 95% CI: 0.31–1.07; p = 0.079, respectively). There were no differences between the IPT and IST arms with regard to mean difference in haemoglobin or parasite density among participants with *Pf* infection.

More than 72% of participants (541–546 out of 746) were included in selective attention, literacy, and numerical tests as part of the cognitive and educational outcomes assessments. Because participants in grade levels 1 and 2 were not included, only 60% (450/746) participated in code transmission test assessments. There were no differences in the rates of participation by study arm (Table S6). There was no statistical difference between IPT or IST arms compared to the

control arm in sustained attention measured as the difference in mean scores on the code transmission test or in selective attention (Table 3). However, participants in the IST and IPT arms scored higher in the literacy assessment than the control arm with a mean increase of 3.67 points (95% CI: 0.02, 7.32; p-value 0.049) and 3.30 points (95% CI: –0.34, 6.94; p-value 0.076), respectively. When combined and compared to control, the intervention arms had an increase of 3.48 points (95% CI: 0.32, 6.65; p-value 0.031) on the literacy test (Table S7). Although not statistically different, the mean scores for numeracy assessment were also higher in both intervention arms compared to control. There were no differences in cognitive or educational outcomes comparing between intervention arms (IPT vs IST).

There were no serious adverse events (AEs) reported during the study. In total, there were 96 Grade 1–2 AEs (mild to moderate) reported in 4.7% of participants (35/746) (Table 4). No AEs were reported in the control arm. AEs were more common in the IPT arm compared to the IST arm and among participants who received CQ compared to DP. The most common adverse events included dizziness, headache, nausea, and abdominal pain.

Characteristics assessed at enrolment	Control (n = 249)	IPT (n = 249)	IST (n = 248)	Total (n = 746)
Age, y, mean (SD)	11.3 (3.2)	11.4 (3.1)	11.3 (3.2)	11.3 (3.2)
Female, n (%)	134 (54)	136 (55)	145 (58)	415 (56)
Female (≥10 years old), n (%)	77 (58)	94 (69)	93 (64)	264 (64)
Household owns at least one LLIN, n (%)[a]	135 (54)	127 (51)	125 (50)	387 (52)
Household head education, n (%)[b]				
No school	23 (9)	27 (11)	21 (8)	71 (10)
Primary school only	173 (69)	163 (65)	165 (67)	501 (67)
Beyond primary school[c]	44 (18)	49 (20)	51 (21)	144 (19)
Missing or don't know	9 (4)	10 (4)	11 (4)	30 (4)
Socioeconomic group, tertials, n (%)				
Low	78 (31)	90 (36)	76 (31)	244 (33)
Medium	83 (33)	80 (33)	86 (35)	232 (34)
High	88 (36)	77 (31)	82 (33)	247 (33)
Assessed at the first intervention visit	**(n = 227)**	**(n = 233)**	**(n = 234)**	**(n = 694)**
Reported fever in the last 2 days, n (%)[b]	69 (30)	62 (27)	76 (33)	207 (30)
Reported level of wellness, n (%)[b]				
Very well	171 (75)	160 (69)	167 (71)	498 (72)
Pretty well	14 (6)	24 (10)	23 (10)	61 (9)
A little unwell	27 (12)	36 (16)	32 (14)	95 (14)
Sick	15 (7)	12 (5)	11 (5)	38 (5)
Reported sleeping under a bed net last night, n (%)[b]	102 (45)	106 (46)	118 (51)	326 (47)
Haemoglobin, g/dL, mean (SD)	12.6 (1.23)	12.7 (1.33)	12.6 (1.27)	12.7 (1.28)
Anaemic, n (%)	49 (22)	50 (22)	50 (21)	149 (22)
Pf infection by PCR, n (%))[b,d]	127 (56)	120 (53)	107 (46)	354 (52)
Mean log-parasite density, (SD) (for those PCR positive)	2.88 (1.97)	2.37 (1.91)	2.70 (2.09)	2.65 (1.99)

Baseline characteristics of participants in a randomized clinical trial comparing IPT and IST to control (standard of care) in a primary school in rural Malawi. IPT, Intermittent Preventive Treatment; IST, Intermittent Screening and Treatment; *Pf*, *Plasmodium falciparum*; SD, Standard Deviation; LLIN, Long Lasting Insecticide Treated Net; PCR, Polymerase Chain Reaction. [a]746 enrolled students originated from 698 households. This occurred because some of the students were siblings or otherwise related, leading to the sharing of households. However, despite residing together, each student's household-level data was recorded individually and distinctly hence 746 households reported. [b]Missing values: Household head education level (n = 30), Reported wellness (n = 54, younger children who did not understand the question), Reported sleeping under a bed net last nice (n = 2), PCR results (n = 7). [c]Primary school ends after grade 8. [d]Anaemia was defined using WHO recommended age and gender specific thresholds.

Table 1: **Participant characteristics assessed at either enrolment or the first intervention visit by study arm.**

Discussion

In this trial, IPT administered to schoolchildren at 6-week intervals three times during the peak transmission season protected children from *Pf* infections, clinical malaria, and anaemia compared to control. IST reduced *Pf* infections and increased haemoglobin but did not decrease anaemia or the incidence of clinical malaria compared to control. These findings are consistent with prior meta-analyses of the health impact of school-based preventive treatment across sub-Saharan Africa.[29] This study, the first clinical trial in schoolchildren to compare IPT and IST as two approaches to malaria chemoprevention, shows that in our setting IPT has additional benefits compared to IST. The limited efficacy of IST on clinical malaria and anaemia is consistent with the only prior school-based trial of IST and with studies comparing IPT and IST in pregnant women.[16,30] Further, the IST arm in our trial addressed limitations in the prior school-based trial of IST by utilizing a higher sensitivity diagnostic, taking place in an area of high transmission, and using longer-acting treatment drugs, but still demonstrated additional benefits of IPT suggesting the importance of clearing all infections and providing a period of prophylaxis against new infections for all students.

As anticipated for a short term intervention, we observed modest impacts of the interventions on our secondary cognitive and educational outcomes. The code transmission test measuring sustained attention is the only cognitive assessment previously used in multiple studies.[15,31] We included it to facilitate comparisons to prior studies, but did not detect a difference in sustained attention in either intervention arm compared to control. Because the paper-based code transmission test requires writing numbers, participants in the lowest grade-levels were unable to complete the assessment. Therefore fewer participants were able to participate and we were unable to measure sustained attention in the youngest and potentially most vulnerable age group. In contrast, tablet-based self-assessments of selective attention and foundational skills in literacy and math were successfully administered to all age groups with minimal training even in this population who had limited to no prior exposure to tablets and smart phones. While we did not detect a difference in selective

Outcome	Control n = 240		IPT n = 243				IST n = 244				IPT vs. IST	
	Number positive	Proportion	Number positive	Proportion	aOR compared to control [95% CI]	p-value	Number positive	Proportion	aOR compared to control [95% CI]	p-value	aOR [95% CI]	p-value
Pf infection PCR[a,b,c]	127	0.53	41	0.17	0.18 [0.11, 0.27]	<0.0001	58	0.24	0.27 [0.18, 0.40]	<0.0001	0.66 [0.42, 1.02]	0.065
Anaemia[a,d]	36	0.15	20	0.08	0.49 [0.27, 0.91]	0.023	32	0.13	0.85 [0.50, 1.47]	0.57	0.58 [0.31, 1.07]	0.079
	Mean	**SD**	**Mean**	**SD**	**Mean difference compared to control [95% CI]**	**p-value**	**Mean**	**SD**	**Mean difference compared to control [95% CI]**	**p-value**	**Mean Difference**	**p-value**
Log parasite density for those PCR positive[a,e]	2.68	2.09	2.24	2.37	−0.45 [−1.21, 0.31]	0.24	2.27	2.29	−0.4 [−1.11, 0.23]	0.20	−0.01 [−0.85, 0.87]	0.98
Haemoglobin (g/dL)[a,f]	13.08	1.46	13.35	1.38	0.25 [0.01, 0.48]	0.041	13.34	1.45	0.28 [0.04, 0.51]	0.021	−0.03 [−0.26, 0.20]	0.80
	Cases	**Incidence rate [95% CI]**	**Cases**	**Incidence rate [95% CI]**	**IRR compared to control [95% CI]**	**p-value**	**Cases**	**Incidence rate [95% CI]**	**IRR compared to control [95% CI]**	**p-value**	**IRR [95% CI]**	**p-value**
Clinical malaria[g,h]	99	0.51 [0.42, 0.62]	38	0.19 [0.14, 0.27]	0.38 [0.26, 0.55]	<0.0001	107	0.56 [0.46, 0.68]	1.09 [0.83, 1.44]	0.52	0.35 [0.24, 0.50]	<0.0001

Health outcomes measured either at the outcome visit or throughout the implementation of three rounds of school-based IPT or IST among primary school students in rural Malawi. IPT, Intermittent Preventive Treatment; IST, Intermittent Screening and Treatment; *Pf*, *Plasmodium falciparum*; SD, Standard Deviation; aOR, adjusted odds ration; IRR, Incidence rate ratio; CI, Confidence intervals; PCR, Polymerase Chain Reaction. [a]Measured 6–8 weeks after the final intervention. [b]PCR results were missing for two students in each of the control and IPT arms. [c]Logistic regression model comparing groups with respect the presence of *Pf* infections, adjusting for students' grade-level. [d]Logistic regression model comparing groups with respect to proportion anaemic at the outcome visit, adjusting for anaemia at the first intervention visit and student's grade level. [e]Linear regression model for mean of log *Pf* densities at the outcome visit, adjusting for students' grade-level. [f]Multivariable ANCOVA model comparing mean haemoglobin levels at the outcome visit, adjusting for haemoglobin level at intervention visit-1, age, and sex. [g]Measured from each individual's first intervention visit until their outcome visit. Total follow-up time was 285.6 person-years (control 96.1, IPT 94.2, IST 95.3 person-years). [h]Poisson Regression model comparing episodes of clinical malaria cases from first intervention visit until final outcome visit. Results are report as rate per 6 months.

Table 2: **Effect of three rounds of school-based intermittent preventive treatment (IPT) and intermittent screening and treatment (IST) on health outcomes.**

attention or math, the improvement in literacy is encouraging. Our results may not reflect a true absence of effect on cognition or math for several reasons. Attention is a single domain of cognitive function. We chose to measure attention based on prior studies, but broader assessments of cognitive function may be needed to detect differences. Our study measured outcomes after only one year of intervention; more time may be required to accumulate measurable impact on cognition and math. Our observed improvement in literacy could reflect skill acquisition in reading is more immediate or that our literacy assessment was more sensitive to change than other metrics. Future trials of longer duration, using broader assessments of cognitive function, and with cognitive and educational endpoints as primary outcomes are needed to better quantify the impact of malaria chemoprevention on learning. Our experience suggests that self-administered, tablet-based assessments could be used in larger-scale evaluations of the impact of health interventions on cognitive and educational outcomes in this age group. The health of the learner is increasingly recognized as critical for educational attainment.[32,33] Indeed, for the first time, health interventions are included among the World Bank's Cost-effective approaches to improve global learning.[34] Thus we advocate for prioritizing school-age children in malaria chemoprevention programs and for including education outcomes in assessments of the full economic evaluations of health interventions in this age group.

Overall, school-based chemoprevention was safe, well-tolerated as there were no serious AEs, and, based on community and school feedback meetings, well received by community and school stakeholders. The more frequent AEs reported by participants receiving CQ is challenging to interpret given that CQ was only administered to adolescent girls to avoid the risk of administering artemisinin-based treatment in an undetected pregnancy. Due to the sensitivity of adolescent pregnancy in the study community and unreliability of self-report of early pregnancy, we decided to administer CQ to all girls ten years old and older who were likely to have been begun menses. While sensitivity around pregnancy and menses as well as risks associated with chemoprevention should be locally determined, adolescent girls are a critical population to protect with chemoprevention as adolescent pregnancies are at highest risk of adverse consequences of malaria in pregnancy[35]

Outcome	Control		IPT				IST				IPT vs IST	
	N	Mean (SD)	N	Mean (SD)	Mean difference compared to control [95% CI]	p-value	N	Mean (SD)	Mean difference compared to control [95% CI]	p-value	Mean difference [95% CI]	p-value
Single-digit Code Transmission (Grades 3–4)	69	14.5 (5.6)	74	15.5 (4.7)	0.87 [−0.92, 2.66]	0.34	75	14.8 (6.5)	0.31 [−1.48, 2.09]	0.74	0.56 [−1.19, 2.32]	0.53
Single-digit and double-digit Code transmission (Grades 5–8)	74	31.7 (6.4)	79	32.2 (5.6)	0.51 [−1.48, 2.50]	0.61	79	30.6 (7.5)	−1.02 [−3.01, 0.97]	0.31	1.53 [−0.42, 3.49]	0.12
Selective attention	177	2.5 (5.7)	180	2.6 (5.4)	0.19 [−0.93, 1.31]	0.74	184	2.3 (5.4)	−0.12 [−1.24, 0.99]	0.83	0.31 [−0.80, 1.43]	0.58
Literacy	179	83.7 (37.6)	184	90.0 (35.9)	3.30 [−0.34, 6.94]	0.076	183	89.8 (35.8)	3.67 [0.02, 7.32]	0.049	−0.37 [−3.99, 3.25]	0.84
Numeracy	177	35.9 (15.4)	183	37.7 (15.3)	0.66 [−1.02, 2.33]	0.44	182	37.1 (15.0)	0.34 [−1.34, 2.02]	0.69	0.32 [−1.35, 1.98]	0.71

Cognitive and learning outcomes measured 6–8 weeks after implementation of three rounds of school-based IPT or IST among primary school students in rural Malawi. Generalized linear models comparing each intervention group to control with respect to each of the scores for each outcome in this table, adjusting students' grade-level. Target grade-levels and missing data by study arm are presented in Table S4. p-values unadjusted for multiple comparisons are presented to evaluate the strength of individual associations. Because two comparisons were made for cognitive function (sustained and selective attention) and foundational educational skills (literacy and numeracy), p-value <0.025 would be considered significant using the Bonferroni approach.

Table 3: **Effect of three rounds of school-based intermittent preventive treatment (IPT) and intermittent screening and treatment (IST) on cognition and education outcomes.**

and are likely to receive the least antenatal care.[36] Chloroquine is an attractive solution for this sub-population given its long history of safety and return of susceptibility in multiple highly endemic areas.[37] While widespread use of CQ monotherapy should be avoided, targeted use in this high-risk population is unlikely to lead to widespread drug resistance.

While our trial was successfully implemented and had excellent follow-up of participants, there are limitations to consider in interpretation of the results. First, the lack of a placebo control group may have resulted in an overestimation of the effect of the IPT on clinical malaria due to the awareness of receiving no treatment leading to changes in treatment seeking in the control arm and, to a lesser extent, the IST arm. To mitigate this bias, participants in all arms were encouraged to seek treatment when symptomatic. Second, there was a potential for performance bias in the some of the outcome assessments since participants and assessors were not masked. However, primary outcome assessments were done by blinded laboratory technicians and clinicians at the health centre were blinded, and the use of tablets and administering tests in mixed groups by study arm for cognitive and education assessments may have reduced this bias. Third, deletions of HRP2 gene in *Pf* could have resulted in false negative results and undertreatment in the IST arm, which may have biased the effect of the intervention towards the null. Although there is limited evidence on the prevalence of *Pf* HRP2 gene deletions in Malawi, evidence of their existence in some sub-Saharan African countries, including neighbouring Tanzania, warrants further investigation.[38] Despite the consistency of our findings with the prior trial of IST and our optimization of the IST approach, there may still be other transmission settings were the IST approach is efficacious.[16] Our findings add additional data which could be useful in modelling to identify these settings. Fourth, because school-age children are a primary source of human-to-mosquito parasite transmission, the control arm may have been inadvertently protected from infection due to local reductions in transmission as a 'spillover' effect in our individually randomized trial. Participants in the intervention arms represent only ~25% of the school enrolment. Therefore, we expect spillover to be minimal. However any spillover that did occur would bias results toward the null hypotheses. While a cluster randomized design would limit spillover and allow quantification of the potential indirect effect on transmission, the scale and expense of a cluster randomized design were not feasible with current funding. Finally, the study period may have been too short to observe the full potential impact of the intervention on cognition and education outcomes.

Symptoms	Total n (%)	By study arm n (%)		By drug received n (%)	
		IPT	IST	CQ	DP
Dizziness	17 (18)	9 (13)	8 (28)	13 (23)	4 (10)
Headache	17 (18)	11 (16)	6 (21)	6 (10)	11 (28)
Nausea	16 (17)	12 (18)	4 (14)	13 (23)	3 (8)
Abdominal pain	14 (15)	10 (14)	4 (14)	8 (14)	6 (15)
Fever	8 (8)	5 (7)	3 (10)	2 (3)	6 (15)
Weakness	8 (8)	6 (9)	2 (7)	4 (7)	4 (10)
Vomiting	5 (5)	5 (7)	0 (0)	4 (7)	1 (3)
Unknown	4 (4)	3 (5)	1 (3)	1 (2)	3 (8)
Heart Palpitations	3 (3)	2 (3)	1 (3)	3 (5)	0 (0)
Anorexia	2 (2)	2 (3)	0 (0)	1 (2)	1 (3)
Altered mental status	1 (1)	1 (2)	0 (0)	1 (2)	0 (0)
Heaviness of eyes, blurred vision	1 (1)	1 (2)	0 (0)	1 (2)	0 (0)
Total	96	67 (70)	29 (30)	57 (59)	39 (41)

Adverse events reported during three rounds of school-based IPT or IST among primary school students in rural Malawi. IPT, Intermittent Preventive Treatment; IST, Intermittent Screening and Treatment; CQ, Chloroquine; DP, dihydroartemisinin-piperaquine.

Table 4: **Frequency of adverse events by students' intervention arm and drugs received as reported by 35 participants who experienced them.**

Our findings suggest that in a clinical trial setting implementing school-based IPT with DP can effectively reduce *Pf* infections, incidence of clinical malaria, and prevalence of anaemia among schoolchildren residing in regions with moderate to high malaria transmission. Although our study was implemented in a single school in rural Malawi, these findings may be generalizable to schoolchildren in rural public primary schools in other sub-Saharan African regions with similar transmission patterns and intensities. During our study, trained study nurses administered study drugs. However, if this approach is adopted and expanded, teachers and or community health workers would likely be engaged in drug distribution. In Malawi, some primary school teachers already provide malaria testing and treatment to symptomatic schoolchildren as a part of the Learner Treatment Kit program.[39,40] Time in motion studies suggest that teachers can deliver health interventions without reduction in instruction time.[41] Additionally, teachers and community health workers play a crucial role in national deworming campaigns, dispensing drugs to schoolchildren as part of their involvement in school health programs.[42] Further implementation and operational research and cost-effectiveness analyses are needed, but other school health interventions suggest school-based malaria chemoprevention is feasible.

In summary, our study provides valuable insights into the efficacy of school-based chemoprevention to reduce the burden of malaria in school-age children. The results support the implementation of IPT, administered every six weeks to boys of all ages and girls under 10 years old using DP, and the use of chloroquine for girls aged 10 and older to avoid risks of other antimalarial drugs in the first trimester of pregnancy. As malaria control efforts continue, further investigations are warranted to address remaining questions related to drug selection, strategies for programmatic implementation, impact on community-level transmission and long-term impact on cognitive and educational outcomes. Our findings contribute to the ongoing discourse on malaria prevention strategies, emphasizing the need for context-specific and evidence-based interventions to reduce the malaria burden among vulnerable populations, particularly schoolchildren in malaria-endemic regions.

Contributors

LMC, MKL, NJP, and DPM conceived and designed the study. AS, MV, and WK collected the data. AS, LSM, and LMC accessed and verified the data. AS, MV, WK, LSM, KBS, and LMC analysed the data. AS, MV, and LMC drafted the first version of the manuscript. All authors saw the draft of the manuscript, contributed to data interpretation, and provided input on writing. All authors critically reviewed the manuscript, had full access to study data, and had the final responsibility to submit for publication.

Data sharing statement

Data will be made publicly available interested researchers should submit a request to the corresponding author.

Declaration of interests

MV is a PhD student under supervision focusing on the links between health, cognition, and learning at the Kamuzu University of Health Sciences (KUHeS), Malawi, and was employed under a service agreement between the Training and Research Unit of Excellence (TRUE) in Malawi and University of Maryland. All other authors declare no competing interests.

Acknowledgements

We are grateful to the participants and their caregivers for their willingness to participate in this study. We would like to thank the study team members, school leaders, and teachers without whose dedication and support the study would not have been as successful. We appreciate the support we received from leaders at the local, district, and national level. We thank onebillion and Imagine Worldwide for enabling our use of onetest and their interest in improving education and the health of learners in Malawi.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102832.

References

1 Health Organization W. World malaria report 2022. https://www.who.int/publications/i/item/9789240086173; 2023. Accessed March 16, 2024.
2 Pullan RL, Bukirwa H, Staedke SG, et al. Plasmodium infection and its risk factors in eastern Uganda. *Malar J*. 2010;9:2. https://doi.org/10.1186/1475-2875-9-2.
3 Walldorf JA, Cohee LM, Coalson JE, et al. School-age children are a reservoir of malaria infection in Malawi. *PLoS One*. 2015;10:e0134061. https://doi.org/10.1371/journal.pone.0134061.
4 Yeka A, Nankabirwa J, Mpimbaza A, et al. Factors associated with malaria parasitemia, anemia and serological responses in a spectrum of epidemiological settings in Uganda. *PLoS One*. 2015;10:e0118901. https://doi.org/10.1371/journal.pone.0118901.
5 Pinchoff J, Chaponda M, Shields TM, et al. Individual and household level risk factors associated with malaria in Nchelenge District, a region with perennial transmission: a serial cross-sectional study from 2012 to 2015. *PLoS One*. 2016;11:e0156717. https://doi.org/10.1371/journal.pone.0156717.
6 Mwandagalirwa MK, Levitz L, Thwai KL, et al. Individual and household characteristics of persons with plasmodium falciparum malaria in sites with varying endemicities in Kinshasa Province, Democratic Republic of the Congo. *Malar J*. 2017;16:456. https://doi.org/10.1186/s12936-017-2110-7.
7 Were V, Buff AM, Desai M, et al. Socioeconomic health inequality in malaria indicators in rural western Kenya: evidence from a household malaria survey on burden and care-seeking behaviour. *Malar J*. 2018;17. https://doi.org/10.1186/s12936-018-2319-0.
8 Touré M, Sanogo D, Dembele S, et al. Seasonality and shift in age-specific malaria prevalence and incidence in Binko and Carrière villages close to the lake in Selingué, Mali. *Malar J*. 2016;15. https://doi.org/10.1186/s12936-016-1251-4.
9 The Institute For Health Metrics and Evaluation. *Global burden of disease (GBD)*; 2019. https://vizhub.healthdata.org/gbd-compare/#. Accessed November 21, 2023.
10 Nankabirwa J, Brooker SJ, Clarke SE, et al. Malaria in school-age children in Africa: an increasingly important challenge. *Trop Med Int Health*. 2014;19:1294–1309. https://doi.org/10.1111/tmi.12374.
11 Chen I, Clarke SE, Gosling R, et al. "Asymptomatic" malaria: a chronic and debilitating infection that should Be treated. *PLoS Med*. 2016;13. https://doi.org/10.1371/journal.pmed.1001942.
12 Nankabirwa J, Wandera B, Kiwanuka N, et al. Asymptomatic Plasmodium infection and cognition among primary school-children in a high malaria transmission setting in Uganda. *Am J Trop Med Hyg*. 2013;88. https://doi.org/10.4269/ajtmh.12-0633.
13 Cohee LM, Peterson I, Buchwald AG, et al. School-based malaria screening and treatment reduces Plasmodium falciparum infection and anemia prevalence in two transmission settings in Malawi. *J Infect Dis*. 2022;226. https://doi.org/10.1093/infdis/jiac097.
14 Cohee LM, Valim C, Coalson JE, et al. School-based screening and treatment may reduce P. falciparum transmission. *Sci Rep*. 2021;11. https://doi.org/10.1038/s41598-021-86450-5.

15 Cohee LM, Opondo C, Clarke SE, et al. Preventive malaria treatment among school-aged children in sub-Saharan Africa: a systematic review and meta-analyses. *Lancet Glob Health*. 2020;8. https://doi.org/10.1016/S2214-109X(20)30325-9.

16 Halliday KE, Okello G, Turner EL, et al. Impact of intermittent screening and treatment for malaria among school children in Kenya: a cluster randomised trial. *PLoS Med*. 2014;11. https://doi.org/10.1371/journal.pmed.1001594.

17 Slater HC, Ross A, Felger I, et al. The temporal dynamics and infectiousness of subpatent Plasmodium falciparum infections in relation to parasite density. *Nat Commun*. 2019;10:1433. https://doi.org/10.1038/s41467-019-09441-1.

18 Watson OJ, Sumner KM, Janko M, et al. False-negative malaria rapid diagnostic test results and their impact on community-based malaria surveys in sub-Saharan Africa. *BMJ Glob Health*. 2019;4. https://doi.org/10.1136/bmjgh-2019-001582.

19 Das S, Jang IK, Barney B, et al. Performance of a high-sensitivity rapid diagnostic test for Plasmodium falciparum malaria in asymptomatic individuals from Uganda and Myanmar and naive human challenge infections. *Am J Trop Med Hyg*. 2017;97:1540–1550. https://doi.org/10.4269/ajtmh.17-0245.

20 World Health Organization. *WHO technical consultation on research requirements to support policy recommendations on highly sensitive point-of-care diagnostics for P. falciparum malaria*. 2018.

21 Kazembe LN, Muula AS, Appleton CC, et al. Modelling the effect of malaria endemicity on spatial variations in childhood fever, diarrhoea and pneumonia in Malawi. *Int J Health Geogr*. 2007;6:33. https://doi.org/10.1186/1476-072X-6-33.

22 RBM partnership to end malaria. Malaria indicator Survey toolkit. https://malariasurveys.org/toolkit.cfm. Accessed March 20, 2024.

23 Howe LD, Galobardes B, Matijasevich A, et al. Measuring socio-economic position for epidemiological studies in low-and middle-income countries: a methods of measurement in epidemiology paper. *Int J Epidemiol*. 2012;41:871–886.

24 Bereczky S, Mårtensson A, Gil JP, et al. Short report: rapid DNA extraction from archive blood spots on filter paper for genotyping of Plasmodium falciparum. *Am J Trop Med Hyg*. 2005;72:249–251. https://doi.org/10.4269/ajtmh.2005.72.249.

25 Hermsen CC, Telgt DSC, Linders EHP, et al. Detection of Plasmodium falciparum malaria parasites in vivo by real-time quantitative PCR. *Mol Biochem Parasitol*. 2001;118:247–251. https://doi.org/10.1016/S0166-6851(01)00379-6.

26 Who, Chan M. *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity*. Geneva, Switzerland: World Health Organization; 2011.

27 Manly T, Robertson I, Anderson V, et al. *Manual for test of everyday attention in children*. London: Thames Valley Test; 1998.

28 Pitchford NJ, Outhwaite LA. Can touch screen tablets be used to assess cognitive and motor skills in early years primary school children? A cross-cultural study. *Front Psychol*. 2016;7. https://doi.org/10.3389/fpsyg.2016.01666.

29 ONEBILLION LEARNERS. onetest. https://onebillion.org/onetest/; 2023. Accessed November 21, 2023.

30 Olaleye A, Okusanya BO, Oduwole O, et al. A systematic review and meta-analysis of dihydroartemisinin-piperaquine versus sulphadoxine-pyrimethamine for malaria prevention in pregnancy. *Int J Gynecol Obstet*. 2019;146:43–55. https://doi.org/10.1002/ijgo.12835.

31 Makenga G, Baraka V, Francis F, et al. Attributable risk factors for asymptomatic malaria and anaemia and their association with cognitive and psychomotor functions in schoolchildren of north-eastern Tanzania. *PLoS One*. 2022;17:e0268654. https://doi.org/10.1371/journal.pone.0268654.

32 Lê F, Diez Roux A, Morgenstern H. Effects of child and adolescent health on educational progress. *Soc Sci Med*. 2013;76:57–66. https://doi.org/10.1016/j.socscimed.2012.10.005.

33 Jackson MI. Understanding links between adolescent health and educational attainment. *Demography*. 2009;46:671–694. https://doi.org/10.1353/dem.0.0078.

34 Global Education Evidence Advisory Panel. Cost-effective approaches to improve global learning: what does recent evidence tell us are 'Smart Buys' for improving learning in low-and middle-income countries?. https://www.edu-links.org/sites/default/files/media/file/GEEAP-Report-Smart-Buys-2023-final.pdf; 2023. Accessed March 8, 2024.

35 Pons-Duran C, Mombo-Ngoma G, Macete E, et al. Burden of malaria in pregnancy among adolescent girls compared to adult women in 5 sub-Saharan African countries: a secondary individual participant data meta-analysis of 2 clinical trials. *PLoS Med*. 2022;19:e1004084. https://doi.org/10.1371/journal.pmed.1004084.

36 Mekonnen T, Dune T, Perz J. Maternal health service utilisation of adolescent women in sub-Saharan Africa: a systematic scoping review. *BMC Pregnancy Childbirth*. 2019;19:366. https://doi.org/10.1186/s12884-019-2501-6.

37 Laufer MK, Thesing PC, Eddington ND, et al. Return of chloroquine antimalarial efficacy in Malawi. *N Engl J Med*. 2006;355:1959–1966. https://doi.org/10.1056/nejmoa062032.

38 Thomson R, Beshir KB, Cunningham J, et al. pfhrp2 and pfhrp3 gene deletions that affect malaria rapid diagnostic tests for Plasmodium falciparum: analysis of archived blood samples from 3 african countries. *J Infect Dis*. 2019;220:1444–1452. https://doi.org/10.1093/infdis/jiz335.

39 Witek-McManus S, Mathanga DP, Verney A, et al. Design, implementation, and evaluation of a training programme for school teachers in the use of malaria rapid diagnostic tests as a part of a basic first aid kit in southern Malawi. *BMC Public Health*. 2015;15:904.

40 Halliday KE, Witek-Mcmanus S, Opondo C, et al. Impact of school-based malaria case management on school attendance, health and education outcomes: A cluster randomised trial in southern Malawi. *BMJ Global Health*. 2020;5:1666.

41 Chinkhumba J, Kadzinje V, Jenda G, et al. Impact of school-based malaria intervention on primary school teachers' time in Malawi: evidence from a time and motion study. *Malar J*. 2022;21:301. https://doi.org/10.1186/s12936-022-04324-1.

42 World Health Organization & World Bank. *WHO-World Bank joint statement: school deworming at a glance*. 2003.