Effectiveness and safety of intermittent preventive treatment with dihydroartemisinin–piperaquine or artesunate–amodiaquine for reducing malaria and related morbidities in schoolchildren in Tanzania: a randomised controlled trial

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Summary

Background In high transmission settings, most school-aged children harbour malaria parasites without showing symptoms, often leading to anaemia and possibly impaired psychomotor and cognitive abilities. We aimed to assess the effectiveness and safety of intermittent preventive treatment for malaria in school-aged children (IPTsc) living in highly endemic areas.

Methods We did an open-label randomised controlled trial in seven primary schools in northeastern Tanzania. Schoolchildren aged 5–15 years were individually randomly assigned (1:1:1) to receive dihydroartemisinin–piperaquine, artesunate–amodiaquine, or standard of care (control) using a balanced block design. Drugs were administered by schoolteachers, with supervision from study nurses, at months 0 (baseline), 4, and 8, and were given in line with manufacturer's recommendations with dose based on the child's bodyweight. The primary endpoints were change from baseline in mean haemoglobin concentration at months 12 and 20, and clinical incidence of malaria and prevalence of parasitaemia at months 12 and 20 in the intervention groups versus the control group. The outcome data were collected through longitudinal surveys conducted every 4 months. Data were analysed on the basis of intention to treat (including all randomised participants) and per protocol (comprising children who completed the full 3-day regimen of all three IPTsc treatment rounds as assigned). This study is registered with ClinicalTrials.gov (NCT03640403).

Findings Of the 1797 children scheduled for clinical screening, 1566 were enrolled and randomly allocated (526 to receive dihydroartemisinin–piperaquine, 527 to receive artesunate–amodiaquine, and 513 to receive standard of care). Due to COVID-19-related school closures, only two schools were visited at month 12 (135 children in the dihydroartemisinin–piperaquine group, 131 in the artesunate–amodiaquine group, and 118 in the control group). At month 12, compared with the control group, the change from baseline in mean haemoglobin concentration was increased by 0·5 g/dL (95% CI 0·2 to 0·8; p<0·0001) in the dihydroartemisinin–piperaquine group and 0·5 g/dL (0·2 to 0·7; p=0·0020) in the artesunate–amodiaquine group in the intention-to-treat analysis (with similar findings in the per protocol analysis). In the same period, in the intention-to-treat analysis, the prevalence of malaria parasitaemia increased from 28·5% (138 of 485 participants) to 33·6% (39 of 116) in the control group, but decreased from 28·0% (139 of 497) to 12·0% (15 of 125) in the dihydroartemisinin–piperaquine group (–21·6 percentage points [95% CI –31·9 to –11·3], p=0·0001 *vs* control at month 12) and from 24·7% (124 of 502) to 16·0% (20 of 125) in the artesunate–amodiaquine group (–17·6 percentage points [–28·4 to –6·9], p=0·0015). The decrease for artesunate–amodiaquine was larger in the per protocol analysis (–25·3 percentage points [–36·3 to –14·2], p<0·0001). The protective effect of IPTsc against malaria parasitaemia was 64% (95% CI 39 to 79; p<0·0001) for dihydroartemisinin–piperaquine and 52% (23 to 70; p=0·0015) for artesunate–amodiaquine in the intention-to-treat analysis, and was slightly higher on per protocol analysis. The protective effect against clinical malaria at month 12 was 20% (95% CI 9 to 29; p=0·0002) for dihydroartemisinin–piperaquine and 19% (8 to 28; p=0·0004) for artesunate–amodiaquine. No significant differences in any primary outcomes between the intervention and control groups were noted at month 20. Dihydroartemisinin–piperaquine and artesunate–amodiaquine were associated with a small number of mild adverse events, and there were no treatment-related serious adverse events or deaths.

Interpretation IPTsc with dihydroartemisinin–piperaquine or artesunate–amodiaquine is a safe and effective approach to reducing malaria parasitaemia, clinical malaria, and related morbidities, and is feasible to implement through programmes delivered by schoolteachers.

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For the Swahili translation of the abstract see **Online** for appendix 1

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Introduction

According to the WHO malaria report 2022,[1] the WHO African Region had an estimated 234 million cases of malaria in 2021, which accounted for about 95% of global malaria cases. Compared with other age groups, school-aged children (5–15 years) have a high prevalence of malaria in most endemic areas of sub-Saharan Africa.[2–5] In most cases, these children remain asymptomatic, which makes them susceptible to anaemia and impaired cognitive ability.[4,6] Reduced haemoglobin concentrations are often a consequence of long durations of infection or recurrent malaria episodes,[7] both of which have been associated with increased gametocyte production[8] that continues to propagate transmission. Control strategies rely mainly on insecticide-treated nets and effective case management with artemisinin combination therapies. However, studies show low use of bednets in school-aged children;[5] thus, a targeted chemopreventive treatment could be a better option for this age group.

Clearing otherwise-untreated asymptomatic infections might provide a window for haematological recovery by decreasing the rate of destruction and removal of parasitised erythrocyte and improving the erythrocyte production rate in the bone marrow.[6] Artemisinin combination therapies are highly effective against the pathogenic asexual parasite stages and immature gametocytes, resulting in a substantial reduction of post-treatment malaria transmission compared with non-artemisinin regimens.[9] Several studies have shown intermittent preventive treatment for malaria in school-aged children (IPTsc) to be a feasible and effective tool[10,11] to prevent clinical malaria and reduce malaria parasitaemia and anaemia in schoolchildren. However, there is still little evidence on the optimal drug and

Research in context

Evidence before this study

Before our study, we conducted a systematic review and meta-analysis to explore the correlation between the malaria parasite carriage in pregnant women and school-aged children living in similar malaria-endemic settings of sub-Saharan Africa. We searched the Malaria in Pregnancy Library, PubMed, Cochrane Library, and Web of Science to include studies indexed or published until Dec 10, 2018. Combinations of the following search terms were used: "children" OR "pregnant women" AND "malaria" OR "*Plasmodium falciparum*" AND "prevalence" AND "Africa". No language or date restrictions were applied to this search. We updated our search to March 31, 2023, by searching PubMed for review articles with the main search terms "malaria prevalence OR burden AND school aged children AND Africa", with no language or date restrictions. Studies showed that most school-aged children (aged 5–15 years) in high transmission settings harbour malaria parasites without showing symptoms, which makes them susceptible to anaemia and impaired cognitive ability. School-aged children were twice as likely to carry malaria parasites as were pregnant women living in the same community, and there was a strong linear correlation between the prevalence of malaria infection in school-aged children and pregnant women (r=0·93, p<0·0001). Despite children being at high risk, with strong correlation to that in their surrounding community, school-aged children still lack targeted interventions tailored to them. Systematic reviews by Cohee and colleagues (2020) and Matangila and colleagues (2015) have shown that intermittent preventive treatment for malaria in school-aged children (IPTsc) is an effective tool to reduce malaria and malaria-related anaemia. These findings support the hypothesis that clearing otherwise untreated, asymptomatic infections might provide a window of opportunity for haematological recovery by decreasing the rate of destruction and removal of parasitised red blood cells and improving the erythrocyte production rate in the bone marrow. However, the optimal drug regimen or schedule for IPTsc has not been established, and most studies have advocated for the use of non-artemisinin combination therapies for IPTsc. In addition, the feasibility of using schoolteachers to implement IPTsc has been minimally investigated.

Added value of this study

We conducted a study with a pragmatic design to mimic how IPTsc could be implemented in Tanzania. We chose artemisinin combination therapy drugs that were registered and used as alternatives to first-line regimens in Tanzanian malaria diagnostics and treatment guidelines, meaning that these drugs were well known and had good safety profiles from a regulatory perspective. We used schoolteachers to administer IPTsc, a strategy that was deemed feasible and effective. We chose a schedule that would provide maximum protective benefit as it mimicked malaria seasonality in the study area. Our design included a second year with no intervention, in which we found no rebound effect, although the benefits obtained in the interventional year disappeared, highlighting a need for sustained IPTsc intervention to maintain the gains in the long term and protect subsequent cohorts.

Implications of all the available evidence

WHO's 2023 guidelines for malaria recommend the use of IPTsc in malaria-endemic settings with moderate to high perennial or seasonal transmission to reduce disease burden. Our findings provide further field-based evidence that malaria control programmes should consider implementing IPTsc. Use of schoolteachers was feasible for IPTsc programmatic implementation and possible integration, as schoolteachers are already used to deliver school-based mass anthelmintic drug administration and nutritional programmes.

schedule for implementation of IPTsc in the context of transmission seasonality and school programmes.

Implementing IPTsc with the first-line drug for treating clinical malaria might not be a good approach, as it could contribute to drug resistance. However, artemisinin partner drugs that have shown antagonistic resistance mechanisms to those of the first-line drug can be considered for preventive strategies.[12] In this study, we used dihydroartemisinin-piperaquine because of its longer prophylactic effect compared with other artemisinin combination therapies and because it is listed as an alternative to first-line treatment of uncomplicated malaria in Tanzania. Artesunate–amodiaquine was chosen for similar reasons and has been shown to have increased sensitivity in areas (including Tanzania) where amodiaquine was banned in the early 2000s.[12] Thus, we undertook an individual randomised controlled trial to investigate the protective effect and safety of IPTsc with either dihydroartemisinin–piperaquine or artesunate–amodiaquine compared with the standard of care (passive detection) against malaria and its morbidities in children attending primary school and living in a highly malaria-endemic area.

Methods

Study design and participants

This was a randomised, controlled, open-label study assessing the safety and effectiveness against anaemia and malaria morbidity of two antimalarial drug-combinations, dihydroartemisinin–piperaquine and artesunate–amodiaquine, compared with no antimalarial chemoprevention (the control group), in children attending school in Muheza, Tanga, northeastern Tanzania. In this area, malaria transmission occurs throughout the year and has two seasonal peaks following the rainy season from December to January and from March to May.[13,14] Participants were recruited from seven primary schools located in seven villages with high malaria prevalence according to a previous malariometric survey.[13] Each village (Pangamlima, Songa Kibaoni, Heinkele, Kwakibuyu, Mhamba, Bwitini, and Mkulumilo) had only one public primary school of 200–550 students. The trial design and protocol have been published previously.[14]

We recruited schoolchildren with no signs or symptoms of malaria. Boys and girls in class 5 or below (aged 5–15 years) who had no clinical features of severe anaemia and no known chronic illness or history of hypersensitivity to the study drugs were enrolled.

The study was granted ethical clearance by the Medical Research Coordinating Committee of Tanzania (approval numbers NIMR/HQ/R.8a/Vol.IX/2818, NIMR/HQ/R.8c/Vol.I/668 [for amendment], and NIMR/HQ/R.8c/Vol.I/1276 [for ethical clearance renewal]). Regulatory approval was obtained from the Tanzania Medicines and Medical Devices Authority (approval number TFDA0017/CTR/0018/07). We also obtained permission from various levels of local government including local school committees. Written informed consent for participation was obtained from children's parents or guardians, and children aged 11 or older were asked to assent.

Randomisation and masking

Children were randomly assigned (1:1:1) to one of three groups: dihydroartemisinin–piperaquine, artesunate–amodiaquine, or control. Randomisation was done with a balanced block design, with the control group used as reference, with an online randomisation service.[15] A block size of six was used to ensure equal representation of each study group. A randomisation list was generated by the data manager and provided to study nurses in sealed envelopes. During enrolment, children were lined up in no particular order in two lines (one for boys and one for girls) before passing through the clinical evaluation room where randomisation took place; every six consecutive pupils from the same class were included in the same randomisation block to ensure balanced allocation per school and class. Pupils deemed eligible by study clinicians were randomly allocated by the study nurse. In a sequential manner, a sealed envelope was opened before each eligible child. The laboratory technicians analysing the samples were masked to the group allocation of the participants because the sample identification details did not show the study group.

Procedures

The interventional treatments were given at 4-month intervals for the first year: at baseline, month 4 (August, 2019), and month 8 (January, 2020; figure 1). A second non-interventional year of follow-up was planned to assess possible rebound effects, and no study drugs were provided during this period; standard treatment guidelines were followed for children who fell ill with malaria. Dihydroartemisinin–piperaquine and artesunate–amodiaquine were administered orally, in line with study group allocation, as a full therapeutic dose (3-day course) according to the child's body-weight, following the manufacturer's package insert. Schoolteachers were trained to administer the drugs to children with supervision from study nurses. Dihydroartemisinin (40 mg) and piperaquine (320 mg) tablets (D-Artepp; manufactured by Guilin Pharmaceutical, Shanghai, China) were donated to the study by Guilin Pharmaceuticals Tanzania. Dihydroartemisinin–piperaquine dosage per bodyweight was one tablet for children weighing 11 to <17 kg, one and a half for those weighing 17 to <25 kg, two for those weighing 25 to <36 kg, three for those weighing 36 to <60 kg, and four for those weighing 60 to <80 kg. Artesunate–amodiaquine (one tablet of 50 mg artesunate and 135 mg amodiaquine for children weighing 12 to <18 kg; one tablet of 100 mg artesunate and 270 mg amodiaquine for children weighing 18 to <36 kg, and two of these higher-dose tablets for children weighing ≥36 kg; Winthrop; manufactured by

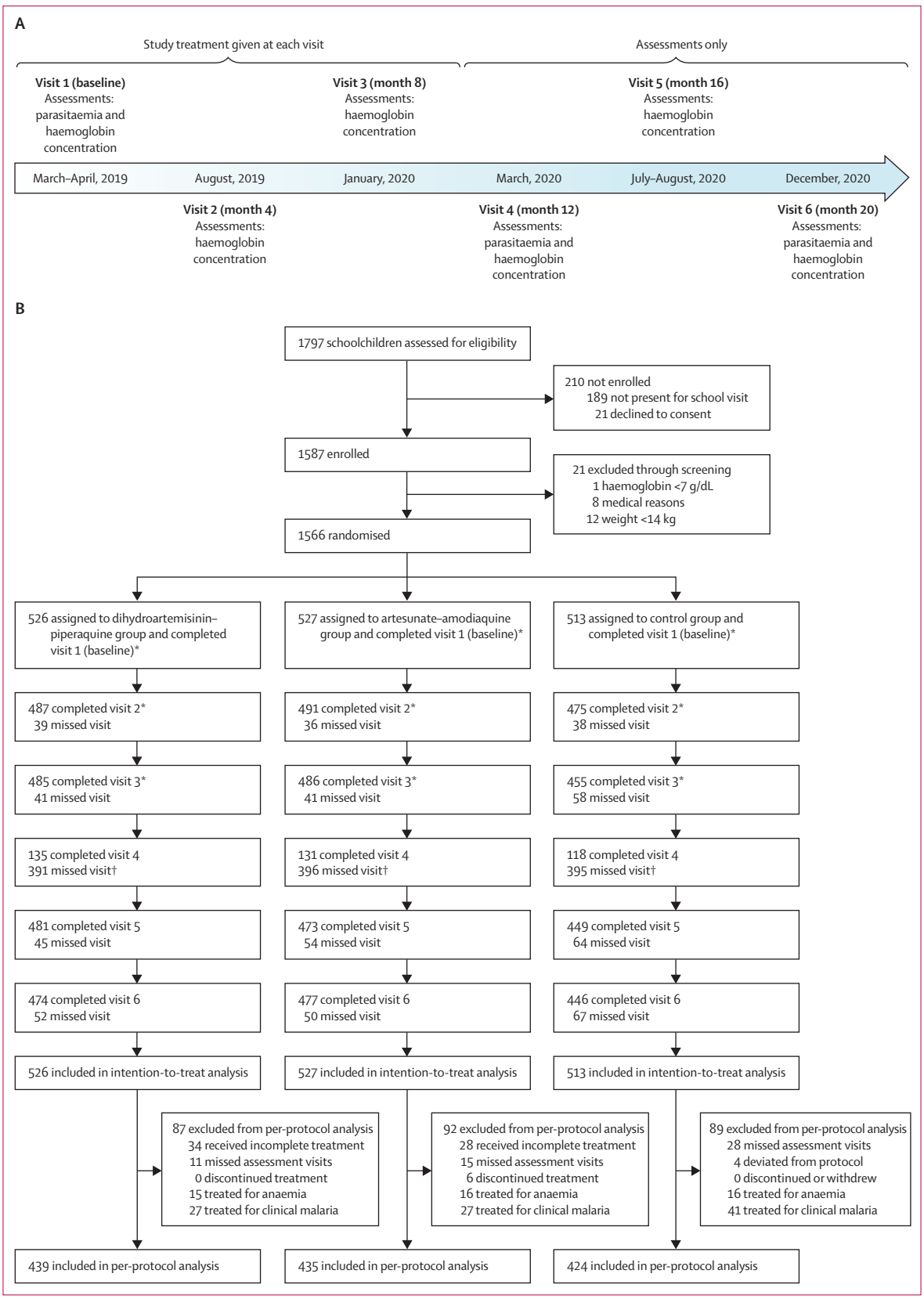

Figure 1: **Study timeline and profile**
Children could continue in the study even if they missed visits. *Intervention was given at these visits (months 0, 4, and 8). †Visit was disrupted by school closure due to COVID-19 pandemic; only two schools were visited before closure.

Sanofi Pharmaceuticals) was procured from an agent or distributor in Kenya. Dihydroartemisinin–piperaquine and artesunate–amodiaquine were WHO prequalified. To account for the possible effect of endemic soil-transmitted helminths and schistosomiasis on anaemia in the study area, all participants were treated with albendazole (400 mg) given orally at baseline and 1 year later during a routine annual mass drug administration by the Tanzanian Neglected Tropical Diseases Control Program.[16] Praziquantel at 40 mg/kg was given orally to children with schistosomiasis.

During follow-up, clinical assessment and testing were done every 4 months for 20 months (six visits; figure 1). Considering convenience related to the school calendar and programme, baseline clinical assessments and testing were done in March–April, 2019 (visit 1), followed by August, 2019 (visit 2), January, 2020 (visit 3; although visit 3 could have been in December 2019, this date was not convenient as children were on annual leave from school). Visit 4 was done in March, 2020; however, this visit was interrupted by the COVID-19 pandemic, which resulted in school closure (only two schools were attended at this timepoint). This interruption was shared across study groups because study participants were individually randomised. Visits 5 and 6 were done in July–August, 2020, and December, 2020, respectively.

At baseline and at each follow-up visit, children underwent a standardised assessment of symptoms and a focused physical examination, including measurement of weight and temperature. Thick and thin blood smears were done to measure malaria parasitaemia using a light microscope, with samples obtained from participants before treatment at baseline, and at months 12 (visit 4) and 20 (visit 6). Malaria parasitaemia prevalence was calculated as the number of children with any parasites (irrespective of species) on thick blood smears divided by the total number of children enrolled and tested.[17,18] Before treatment at baseline and at visits 4 and 6, stool samples were collected to test for soil-transmitted helminths and urine samples to test for schistosomiasis. Haemoglobin concentration was measured with a haemoglobinometer (HemoCue, Ängelholm, Sweden) before study treatment at baseline and each follow-up visit. Anaemia was defined according to WHO age-specific cutoff points for haemoglobin (<11·5 g/dL for children aged 6–11 years, <12·0 g/dL for those aged 12–14 years, <13·0 g/dL for boys aged 15 years, and <12·0 g/dL for girls aged 15 years).[19] Weight and height were assessed at each visit, BMI and other anthropometric index *Z* scores (height-for-age and weight-for-age) were calculated with methods described elsewhere.[17,18]

The study team engaged with three school health teachers, two community health workers, and at least one health facility in the study area to track, manage, and document adverse events and clinical malaria episodes that occurred between visits. The study team collected such reports monthly during routine supervision visits. Any sick child (as reported by parents, guardians, or teachers) was tested for malaria with a malaria rapid diagnostic test (mRDT) before being referred to a nearby hospital for further treatment. The documented malaria episodes were used to ascertain the incidence of clinical disease episodes in accordance with the protocol.[14] All participants had an identification card that contained an identification number, the child's name, and the child's school class. Using this card for identification, the community health worker or health facility worker would identify the participant and record the case on an adverse event form and this information was verified by the study clinicians before being entered into the database. During the consenting process, parents or guardians were instructed that, if their child became sick, they should contact the nearby health facility (preidentified per school) or the community health worker, who would assess whether the child had a febrile illness that warranted testing with an mRDT and, if positive, treatment for malaria. If the mRDT was negative or the child showed signs of severe condition malaria, the child would be referred to the nearby health facility, where clinicians would proceed per local treatment standards. Community health workers did not treat children with severe conditions, but followed up at the health facility to confirm if the child had malaria or not. This information was verified by the study clinicians, who would regularly visit the health facility to obtain relevant information from the hospital register. If parents or guardians took their child directly to the hospital, the health facility in charge would record such cases on special study forms that were collected by study clinicians after verification on the hospital register. This service was provided regardless of the study group to which the child was assigned. The collection of malaria incidence data was not affected by school closures due to COVID-19 pandemic, as the community health workers continued their service in the respective villages or schools.

A 20 m shuttle run test[20] was used to assess the effect of the IPTsc intervention on psychomotor function, and cognitive function was assessed with the Test of Everyday Attention for Children (TEA-Ch) as described by Manly and colleagues.[21] These tests were done on pupils of classes 4 and 5 at baseline and months 12 and 20. Psychomotor function was determined by VO_2max, a measure of how much oxygen an individual uses during exercise at a maximum effort, and was translated as a fitness score.[20] Each fitness score was translated into VO_2max (mL/kg per min) by calculation using a formula described by Leger and colleagues.[20] For sustained attention measured using the TEA-Ch battery, a child could score from 0 to 40. Cognitive and psychomotor are further detailed in the protocol[14] and elsewhere.[17]

Outcomes

In both the intention-to-treat and per protocol analyses, the primary endpoints were change from baseline in

mean haemoglobin concentration at months 12 and 20 of follow-up, and incidence and prevalence of clinical malaria and malaria parasitaemia at months 12 and 20 of follow-up. Secondary study endpoints were anaemia prevalence at months 4, 8, 12, 16, and 20 of follow-up (although initially specified in the protocol as a primary endpoint, it was replaced with malaria prevalence after the basline survey, since anaemia was already reflected by change in haemoglobin); and change from baseline in cognitive and psychomotor scores at months 12 and 20. Other outcomes (which will be reported in separate publications) were improvement in school attendance, prevalence of PCR-confirmed submicroscopic parasitaemia, prevalence of validated common *P falciparum* polymorphisms associated with drug sensitivity, and change in serum antibody responses to *P falciparum* AMA-1 and MSP-1_{19}, all measured at baseline and months 12 and 20.

The study team in collaboration with community health workers and school health teachers monitored adverse events. For each round of IPTsc, children were asked the day after receiving the drug if they had any adverse events since dosing. In addition, children and parents were informed to report any adverse event to the study team through community health workers or

	Intention to treat			Per protocol		
	Dihydroartemisinin–piperaquine group (n=526)	Artesunate–amodiaquine group (n=527)	Control group (n=513)	Dihydroartemisinin–piperaquine group (n=439)	Artesunate–amodiaquine group (n=435)	Control group (n=424)
Age, years						
5–9	296/526 (56·3%)	274/527 (52·0%)	286/513 (55·8%)	238/439 (54·2%)	215/435 (49·4%)	225/424 (53·1%)
10–15	230/526 (43·7%)	253/527 (48·0%)	227/513 (44·2%)	201/439 (45·8%)	220/435 (50·6%)	199/424 (46·9%)
Median	9 (7–11)	9 (7–11)	9 (7–11)	9 (7–11)	10 (8–11)	9 (7–11)
Sex						
Male	278/526 (52·9%)	267/527 (50·7%)	281/513 (54·8%)	230/439 (52·4%)	219/435 (50·3%)	225/424 (53·1%)
Female	248/526 (47·1%)	260/527 (49·3%)	232/513 (45·2%)	209/439 (47·6%)	216/435 (49·7%)	199/424 (46·9%)
History of malaria in the past month	156/524 (29·8%)	180/525 (34·3%)	162/512 (31·6%)	128/437 (29·3%)	147/433 (33·9%)	133/423 (31·4%)
Sleeps under bednet	411/526 (78·1%)	418/527 (79·3%)	408/513 (79·5%)	343/439 (78·1%)	346/435 (79·5%)	338/424 (79·7%)
Socioeconomic status*						
High	183/524 (34·9%)	172/527 (32·6%)	158/512 (30·9%)	151/439 (34·4%)	144/435 (33·1%)	133/424 (31·4%)
Moderate	156/524 (29·8%)	173/527 (32·8%)	171/512 (33·4%)	129/439 (29·4%)	141/435 (32·4%)	139/424 (32·8%)
Low	185/524 (35·3%)	182/527 (34·5%)	183/512 (35·7%)	159/439 (36·2%)	150/435 (34·5%)	152/424 (35·8%)
Parents' educational level						
Secondary school and higher	31/501 (6·2%)	22/508 (4·3%)	38/490 (7·8%)	25/417 (6·0%)	20/417 (4·8%)	29/404 (7·2%)
Primary school	406/501 (81·0%)	426/508 (83·9%)	393/490 (80·2%)	339/417 (81·3%)	348/417 (83·5%)	327/404 (80·9%)
None	64/501 (12·8%)	60/508 (11·8%)	59/490 (12·0%)	53/417 (12·7%)	49/417 (11·8%)	48/404 (11·9%)
Median number of children per household	3 (2–4), N=487	3 (2–4), N=491	3 (2–4), N=467	3 (2–4), N=404	3 (2–4), N=404	3 (2–4), N=383
Median number of rooms per household	3 (3–4), N=498	3 (2–4), N=506	3 (2–4), N=488	3 (3–4), N=413	3 (2–4), N=416	3 (2–4), N=402
Nutritional status						
Weight for age Z score <–2	142/526 (27·0%)	152/527 (28·8%)	136/513 (26·5%)	122/439 (27·8%)	127/435 (29·2%)	111/424 (26·2%)
Height for age Z score <–2	116/526 (22·1%)	112/527 (21·3%)	99/513 (19·3%)	102/439 (23·2%)	99/435 (22·8%)	82/424 (19·3%)
BMI Z score <–2	145/526 (27·6%)	158/527 (30·0%)	136/513 (26·5%)	119/439 (27·1%)	133/435 (30·6%)	109/424 (25·7%)
Study endpoints at baseline						
Mean haemoglobin concentration	11·6 (1·4), N=526	11·6 (1·3), N=527	11·6 (1·4), N=513	11·6 (1·3), N=439	11·7 (1·3), N=435	11·6 (1·4), N=424
Prevalence of anaemia	254/526 (48·3%)	264/527 (50·1%)	261/513 (50·9%)	208/439 (47·4%)	217/435 (49·9%)	212/424 (50·0%)
Prevalence of malaria	139/497 (28·0%)	124/502 (24·7%)	138/485 (28·5%)	116/414 (28·0%)	106/412 (25·7%)	111/402 (27·6%)
Plasmodium falciparum parasite density, parasites per µL	N=135	N=123	N=136	N=114	N=106	N=109
Geometric mean	760·0	713·1	845·6	768·5	686·0	772·1
Mean	4607·8 (22688·6)	6727·4 (45350·2)	2827·2 (2827·1)	5200·0 (24653·1)	7411·8 (48823·5)	2271·8 (3790·5)
Prevalence of soil-transmitted helminths	4/517 (0·8%)	6/518 (1·2%)	6/500 (1·2%)	4/432 (0·9%)	5/427 (1·2%)	5/413 (1·2%)
Prevalence of schistosomiasis	47/513 (9·2%)	40/517 (7·7%)	43/497 (8·7%)	38/429 (8·9%)	33/426 (7·7%)	33/411 (8·0%)

Data are n/N (%), median (IQR), or mean (SD). *Principal component analysis (PCA) was used to categorise children and their respective households into different socioeconomic statuses, with household socioeconomic scores categorised as low, moderate, or high; variables considered in the PCA were type and building material of the house (roof, walls, floor, and ceiling), toilet type, presence of electricity, ownership of radio, mobile phone, bicycle, motorbike, and vehicle, ratio of number of bedrooms to number of house occupants, occupation of head of household, and number of animals and size of land owned by the family.[37]

Table 1: **Baseline characteristics**

school health teachers or through clinicians at local health facilities. These events were recorded and graded accordingly.

Statistical analysis

The planned number of school children was 1602 (534 per study group), a sample size that would provide 90% power (z_{β}=1·282) to detect a change in haemoglobin concentration of 0·2 g/dL (effect size based on a previous study),[22] using a paired *t* test with a type 1 error rate of 0·05 ($z_{1-\alpha}$=1·96), assuming an SD of 1·25 g/dL and a loss to follow-up of 30%. Under the same assumptions, the decreased sample size due to COVID-19-related school closures at visit 4 (n=384) still had 80% power to detect a similar effect size. During the baseline survey and the routine follow-up visits, data were entered directly into REDCap platforms using mobile REDCap tools.[14,23] Paper-based data (from laboratory results) were double-entered by two data entry clerks into a database developed in Microsoft Access 2010 and verified, and consistency checks and analyses were done with STATA version 15.0.

Data were analysed longitudinally, set as panel data in STATA, and the effect of IPTsc on haemoglobin concentrations was assessed with a linear mixed-model analysis, comparing haemoglobin changes within an individual subject and between study groups. Measures for comparison of treatment groups were expressed as prevalence, mean difference, and protective effect. As done previously,[22] protective effect was calculated as 1–(rate ratio [of malaria parasitaemia, clinical malaria, or anaemia])×100%. Kaplan–Meier analysis was used to estimate time to first episode of clinical malaria. 95% CIs were calculated for all outcome of interest using the linear mixed model, and p<0·05 was considered statistically significant when comparing dihydroartemisinin–piperaquine or artesunate–amodiaquine with control, whereas a p<0·025 was considered significant when comparing dihydroartemisinin–piperaquine with artesunate–amodiaquine (presented in appendix 2). Data were analysed on the basis of intention to treat (in which eligible randomised schoolchildren were included) and per protocol (in which children with incomplete or missing dosing, those with concomitant treatment of malaria or anaemia, and those who were not treated according to the randomisation were excluded).

See Online for appendix 2

This study is registered with ClinicalTrials.gov (NCT03640403).

Role of the funding source

The funders of the study had no role in design, data collection, data analysis, data interpretation, or writing of the report.

	Dihydroartemisinin–piperaquine group		Artesunate–amodiaquine group		Control group		Dihydroartemisinin–piperaquine *vs* control group		Artesunate–amodiaquine *vs* control group	
	n	Mean haemoglobin, g/dL (SD)	n	Mean haemoglobin, g/dL (SD)	n	Mean haemoglobin, g/dL (SD)	Difference in mean change in haemoglobin concentration from baseline, g/dL (95% CI)	p value	Difference in mean change in haemoglobin concentration from baseline, g/dL (95% CI)	p value
Interventional period										
Month 0 (baseline)										
Intention to treat	526	11·6 (1·4)	527	11·6 (1·3)	513	11·6 (1·4)	..	..	..	..
Per protocol	439	11·6 (1·3)	435	11·7 (1·2)	424	11·6 (1·4)	..	..	..	..
Month 4										
Intention to treat	487	12·6 (1·4)	491	11·9 (1·5)	475	12·1 (1·5)	0·4 (0·2 to 0·6)	<0·0001	–0·2 (–0·4 to –0·0)	0·0330
Per protocol	433	12·6 (1·4)	420	12·0 (1·4)	422	12·1 (1·5)	0·5 (0·3 to 0·7)	<0·0001	–0·2 (–0·4 to 0·0)	0·0930
Month 8										
Intention to treat	485	11·2 (1·2)	486	12·7 (1·4)	455	11·9 (1·6)	–0·7 (–0·9 to –0·5)	<0·0001	0·8 (0·6 to 1·0)	<0·0001
Per protocol	431	11·2 (1·2)	404	12·7 (1·3)	424	11·9 (1·5)	–0·7 (–0·9 to –0·5)	<0·0001	0·8 (0·6 to 1·0)	<0·0001
Month 12										
Intention to treat	135	11·6 (1·2)	131	11·7 (1·2)	118	11·1 (1·3)	0·5 (0·2 to 0·8)	<0·0001	0·5 (0·2 to 0·7)	0·0020
Per protocol	118	11·6 (1·2)	116	11·7 (1·1)	105	11·1 (1·3)	0·6 (0·3 to 0·9)	<0·0001	0·5 (0·2 to 0·8)	0·0020
Non-interventional period										
Month 16										
Intention to treat	481	11·6 (1·2)	473	11·7 (1·2)	449	11·7 (1·2)	0·0 (–0·2 to 0·1)	0·6840	0·0 (–0·2 to 0·2)	0·9930
Per protocol	425	11·7 (1·2)	440	11·7 (1·2)	392	11·7 (1·2)	0·0 (–0·2 to 0·2)	0·6820	0·0 (–0·2 to 0·1)	0·6440
Month 20										
Intention to treat	474	11·5 (1·2)	477	11·5 (1·3)	446	11·4 (1·3)	0·1 (–0·1 to 0·3)	0·3910	0·1 (–0·1 to 0·3)	0·2770
Per protocol	430	11·6 (1·2)	431	11·6 (1·2)	392	11·5 (1·3)	0·0 (–0·2 to 0·3)	0·6640	0·1 (–0·1 to 0·3)	0·4710

Table 2: **Effect of intermittent preventive treatment for malaria in school-aged children on haemoglobin concentration**

	Prevalence, n/N (%)			Dihydroartemisinin–piperaquine *vs* control group		Artesunate–amodiaquine *vs* control group	
	Dihydroartemisinin–piperaquine group	Artesunate–amodiaquine group	Control group	Percentage points difference (95% CI)	p value	Percentage points difference (95% CI)	p value
Anaemia							
Baseline							
Intention to treat	254/526 (48·3%)	264/527 (50·1%)	261/513 (50·9%)	−2·6 (−8·7 to 3·5)	0·4040	−0·8 (−6·9 to 5·3)	0·8001
Per protocol	208/439 (47·4%)	217/435 (49·9%)	212/424 (50·0%)	−2·6 (−9·3 to 4·0)	0·4415	−0·1 (−6·8 to 6·6)	0·9731
Month 4							
Intention to treat	106/487 (21·8%)	192/491 (39·1%)	172/475 (36·2%)	−14·4 (−20·1 to −8·8)	<0·0001	2·9 (−3·2 to 9·0)	0·3535
Per protocol	91/433 (21·0%)	162/420 (38·6%)	155/422 (36·7%)	−15·7 (−21·7 to −9·7)	<0·0001	1·8 (−4·7 to 8·4)	0·5813
Month 8							
Intention to treat	299/485 (61·6%)	95/486 (19·5%)	187/455 (41·1%)	20·5 (14·3 to 26·8)	<0·0001	−21·6 (−27·3 to −15·8)	<0·0001
Per protocol	266/431 (61·7%)	74/404 (18·3%)	171/424 (40·3%)	21·4 (14·8 to 27·9)	<0·0001	−22·0 (−28·0 to −16·0)	<0·0001
Month 12							
Intention to treat	68/135 (50·4%)	54/131 (41·2%)	71/118 (60·2%)	−9·8 (−22·0 to 2·4)	0·1181	−19·0 (−31·2 to 6·7)	0·0028
Per protocol	61/118 (51·7%)	47/116 (40·5%)	64/105 (61·0%)	−9·3 (−22·2 to 3·7)	0·1644	−20·4 (−33·3 to −7·5)	0·0024
Month 16*							
Intention to treat	224/481 (46·6%)	214/473 (45·2%)	218/449 (48·6%)	−2·0 (−8·4 to 4·4)	0·5452	−3·3 (−9·7 to 3·1)	0·3142
Per protocol	194/425 (45·6%)	196/440 (44·5%)	188/392 (48·0%)	−2·3 (−9·2 to 4·5)	0·5081	−3·4 (−10·2 to 3·4)	0·3242
Month 20*							
Intention to treat	232/474 (48·9%)	238/477 (49·9%)	242/446 (54·3%)	−5·3 (−11·8 to 1·1)	0·1069	−4·4 (−10·8 to 2·1)	0·1847
Per protocol	207/430 (48·1%)	207/431 (48·0%)	210/392 (53·6%)	−5·4 (−12·3 to 1·4)	0·1197	−5·5 (−12·4 to 1·3)	0·1121
Malaria parasitaemia							
Baseline							
Intention to treat	139/497 (28·0%)	124/502 (24·7%)	138/485 (28·5%)	−0·5 (−6·1 to 5·1)	0·8657	−3·7 (−9·3 to 1·8)	0·1820
Per protocol	116/414 (28·0%)	106/412 (25·7%)	111/402 (27·6%)	0·4 (−5·7 to 6·6)	0·8967	−1·9 (−8·0 to 4·2)	0·5434
Month 12							
Intention to treat	15/125 (12·0%)	20/125 (16·0%)	39/116 (33·6%)	−21·6 (−31·9 to −11·3)	0·0001	−17·6 (−28·4 to −6·9)	0·0015
Per protocol	12/109 (11·0%)	13/112 (11·6%)	38/103 (36·9%)	−25·9 (−36·9 to −14·9)	<0·0001	−25·3 (−36·3 to −14·2)	<0·0001
Month 20*							
Intention to treat	123/446 (27·6%)	121/446 (27·1%)	120/426 (28·2%)	−0·6 (−6·5 to 5·4)	0·8458	−1·0 (−7·0 to 4·9)	0·7316
Per protocol	113/408 (27·7%)	100/403 (24·8%)	105/372 (28·2%)	−0·5 (−6·8 to 5·8)	0·8692	−3·4 (−9·6 to 2·8)	0·2820

Table 3: **Effective of intermittent preventive treatment for malaria in school-aged children on prevalence of anaemia and malaria parasitaemia**

Results

At the baseline survey,[17] 1797 children were scheduled for clinical screening, of which 189 did not show up, 21 declined participation, and 21 were excluded on the basis of screening (either because of low bodyweight [12 children], medical reasons [eight children], or low haemoglobin concentration [one child]). 1566 children (97% of the calculated sample size) were enrolled and randomly allocated to the three study groups: dihydroartemisinin–piperaquine (n=526), artesunate–amodiaquine (n=527), and control (n=513). The overall loss to follow-up across all study visit was 18·8% (1767 of 9396 visits missed). Across the three groups, 113 (7%) missed visit 2, 140 (9%) missed visit 3, 1182 (75%) missed visit 4 (when follow-up was affected by COVID-19-related school closures, and only two schools, Pangamlima and Songa-kibaoni[17] [n=384], were attended before the closures occurred), 163 (10%) missed visit 5, and 169 (11%) missed visit 6 (due to outmigration [n=78], dropout [n=6], absenteeism [n=84], distributed evenly across groups, and death [n=1], which occurred in the control group). Absenteeism was mainly due to farming activities coinciding with scheduled study visits, especially during rainy seasons.

1566 schoolchildren were included in the intention-to-treat analyses and 1298 in the per protocol analyses (table 1), with no significant differences in baseline characteristics between study groups in either analysis. The baseline characteristics of participants can be found in a previously published paper.[17] A further description of baseline characteristics of schoolchildren missing month 12 (five schools) and those who were attended (two schools) is shown in appendix 2 (p 4; further detailed outcome analysis for the two schools is shown on pp 14–20).

Compared with the control group, change from baseline in mean haemoglobin concentration at month 12 was significantly higher in the dihydroartemisinin–piperaquine group (0·5 g/dL [95% CI 0·2–0·8], p<0·0001 in the intention-to-treat analysis; 0·6 g/dL [0·3–0·9], p<0·0001 in

the per protocol analysis) and in the artesunate–amodiaquine group (0·5 g/dL [0·2–0·7], p=0·0020 in the intention-to-treat analysis; 0·5 g/dL [0·2–0·8], p<0·0001 in the per protocol analysis; table 2). However, the change in mean haemoglobin across timepoints was not smooth in the dihydroartemisinin–piperaquine group compared with the control group, with a significantly higher change from baseline at month 4 but a significant decrease at month 8 (table 2; appendix 2 p 5). The artesunate–amodiaquine group showed a smooth increase in mean haemoglobin concentration from baseline to month 8, although the increases were slightly smaller than those in the control group at month 4 and significant increases versus the control group were found only at months 8 and 12. During the non-interventional period (months 16 and 20), the respective changes in mean haemoglobin concentration were not significantly different from those in the control group (table 2; appendix 2 p 5).

IPTsc significantly reduced malaria parasitaemia. At month 12, after three rounds of IPTsc administration, the prevalence of malaria parasitaemia was reduced by 21·6 percentage points (95% CI 11·3–31·9; p<0·0001) compared with the control group in the intention-to-treat analysis and by 25·9 percentage points (14·9–36·9; p<0·0001) in the per protocol analysis in the dihydroartemisinin–piperaquine group. In the artesunate–amodiaquine group, the reduction was 17·6 percentage points (6·9–28·4; p=0·0015) compared with the control group in the intention-to-treat analysis and 25·3 percentage points (14·2–36·3; p<0·0001) in the per protocol analysis. When we assessed the rebound effect in the year following the intervention, by month 20, the prevalence of malaria parasitaemia in all study groups had returned to baseline prevalence (table 3).

The protective effect of dihydroartemisinin–piperaquine against malaria parasitaemia was 64% (95% CI 39–79; p=0·0001) in intention-to-treat analysis and 70% (46–84; p<0·0001) in the per protocol analysis at month 12 (figure 2). The respective protective effect of artesunate–amodiaquine was 52% (23–70; p=0·0015) in the intention-to-treat and 68% (44–82; p<0·0001) in the per protocol analysis (figure 2). The number needed to treat (NNT) to prevent one case of malaria parasitaemia was 5 (95% CI 3–9; p<0·0001) for dihydroartemisinin–piperaquine and 6 (4–15; p=0·0015) for artesunate–amodiaquine in the intention-to-treat analysis. In the per protocol analysis, the NNT was 4 (3–7; p<0·0001) for both interventions. At month 20, IPTsc showed no significant protective effect against malaria parasitaemia (appendix 2 pp 8, 21).

Following the first round of IPTsc, the protective effect against clinical malaria was 29% (95% CI 9 to 44; p=0·0022) for the dihydroartemisinin–piperaquine group and 19% (–2 to 36; p=0·0314) for the artesunate–amodiaquine group (appendix 2 p 8). The person-time survived without event was significantly longer in the dihydroartemisinin–piperaquine group (263·3 days) and artesunate–amodiaquine group (258·7 days) than in the control group (205·8 days; appendix 2 p 8). The mean number of days to first episode of clinical malaria was 64 days (95% CI 60–67) for the dihydroartemisinin–piperaquine group, 59 days (55–64) for the artesunate–amodiaquine group, and 45 days (40–50) for the control group, and was significantly different when comparing each dihydroartemisinin–piperaquine and artesunate–amodiaquine groups against the control group (appendix 2 p 20).

In each round of IPTsc, the clinical malaria incidence rates were lower in the intervention groups than in the control group (appendix 2 p 8). The overall protective effect against IPTsc on clinical malaria after three rounds of IPTsc administration in a 12-month period was 20% (95% CI 9–29; p=0·0002) for dihydroartemisinin–piperaquine and 19% (8–28; p=0·0004) for artesunate–amodiaquine in the intention-to-treat analysis (appendix pp 8, 21). The NNT to prevent one case of clinical malaria in the entire year was 38 (95% CI 25–85; p=0·0002) for

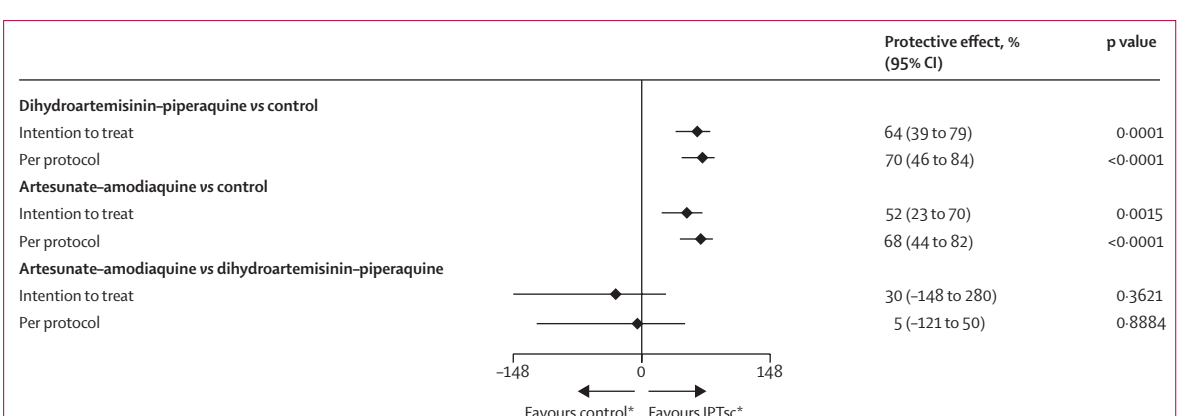

Figure 2: **Protective effect of IPTsc against malaria parasitaemia in schoolchildren at month 12 of intervention**
IPTsc=intermittent preventive treatment for malaria in school-aged children. *For the comparison between the two IPTsc regimens, negative values favour dihydroartemisinin–piperaquine and positive values favour artesunate–amodiaquine.

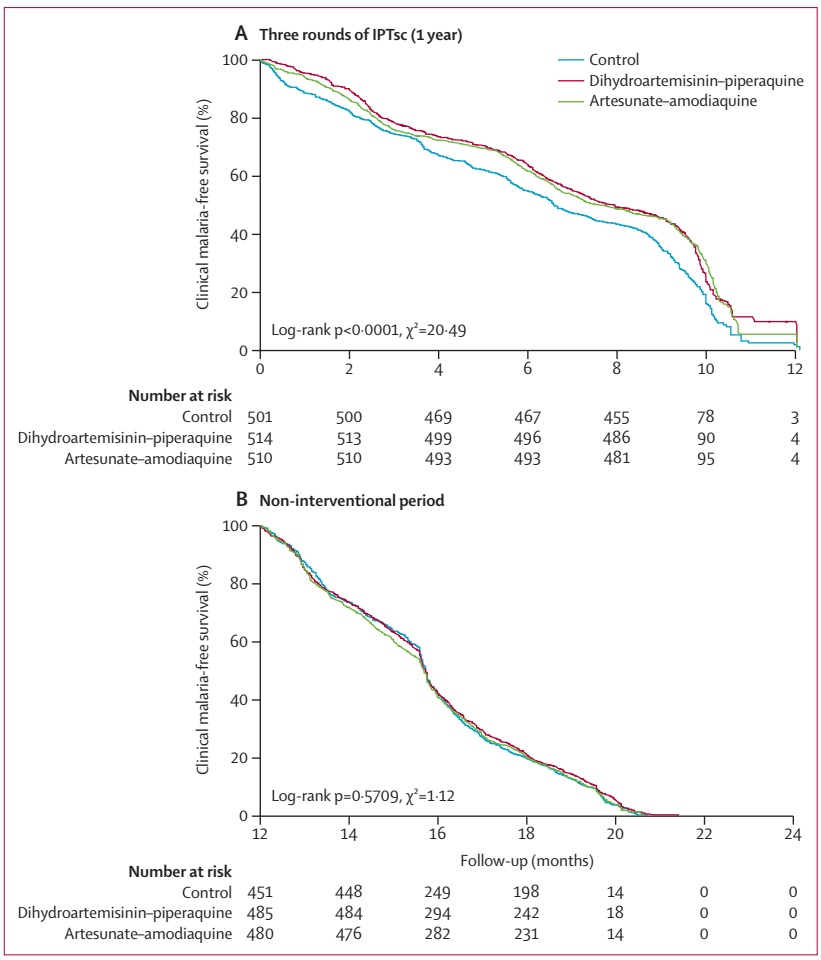

Figure 3: **Time to first episode of clinical malaria following IPTsc**
Kaplan-Meier curves show clinical malaria-free survival throughout the first three rounds of IPTsc in a 12-month period (A) and during the non-interventional period following the initial year of IPTsc administration (B). IPTsc was administered at months 0, 4, and 8. Children who already had clinical malaria at the start of the analysis period were censored at time 0, and thus not shown in the graphs. IPTsc=intermittent preventive treatment for malaria in school-aged children.

dihydroartemisinin–piperaquine and 40 (25–97; p=0·0004) for artesunate–amodiaquine.

The survival estimates were significantly higher in the dihydroartemisinin–piperaquine and artesunate–amodiaquine groups than in the control group after three rounds of IPTsc (up to month 12; log-rank p<0·0001; figure 3A). However, there was no effect noted in the non-interventional year (months 12–20; log-rank p=0·5709; figure 3B). Further analysis using Cox regression is described in appendix 2 (p 9).

At month 12, compared with the control group, the difference in prevalence of anaemia in the dihydroartemisinin–piperaquine group was non-significant in the intention-to-treat analysis (–9·8 percentage points [95% CI –22·0 to 2·4], p=0·1181) and per protocol analysis (–9·3 [–22·2 to 3·7], p=0·1644), whereas the artesunate–amodiaquine group showed a significant reduction in the intention-to-treat analysis (–19·0 percentage points [–31·2 to –6·7], p=0·0028) and per protocol analysis (–20·4 percentage points [–33·3 to –7·5], p=0·0024; table 3). The protective effect of IPTsc against anaemia following three rounds (month 12) of dihydroartemisinin–piperaquine medication was not significant (16% [95% CI –5 to 33], p=0·1181), whereas artesunate–amodiaquine showed protective effect of 32% (12 to 47; p=0·0028) at the same timepoint in the intention-to-treat analysis (appendix 2 p 7). Based on artesunate–amodiaquine being administered three times per year, the NNT to prevent one case of anaemia was 5 (95% CI 3–15; p=0028; intention-to-treat analysis). There were no significant effects on anaemia at months 16 and 20, when no medications were provided (appendix 2 pp 7, 21).

In the linear mixed regression model, there was no significant effect of IPTsc on cognitive or psychomotor function (appendix 2 p 10). However, on multivariate analysis (appendix 2 p 10), boys had significantly higher mean cognitive scores (2·8 [95% CI 0·2–5·4], p=0·0401) than girls at all timepoints. Likewise, psychomotor function was associated with older age, male sex, and number of successive visits. Boys had higher mean VO_2max scores (5·2 [95% CI 4·2–6·2], p<0·0001) than girls at all assessment time points, unrelated to the IPTsc intervention. On per protocol analysis, increased haemoglobin concentration was associated with an increase in unadjusted VO_2max at a coefficient of 0·5 (95% CI 0·0–1·0; p=0·0470).

On drug administration days, 30 adverse events were recorded in the intervention groups (16 in the dihydroartemisinin–piperaquine group and 14 in the artesunate–amodiaquine group), all of which were mild, except for one case of skin rash that was deemed moderate (appendix 2 p 12). These events were deemed to be drug-related and were expected on the basis of drug packet inserts. During the follow-up period, we recorded five serious adverse events unrelated to the study drugs: three in the control group (two cases of severe malaria and one case of septicaemia), one in the dihydroartemisinin–piperaquine group (herbal intoxication), and one in the artesunate–amodiaquine group (severe malaria). All participants recovered well, except for one child in the control group, who had two serious adverse events (severe malaria) on separate occasions, and died after the second episode due to severe anaemia, possibly secondary to severe malaria. All events were reported to the Medical Research Coordination Committee and to the Tanzania Medicines and Medical Devices Authority.

Compliance with prescribed medication was satisfactory as trained schoolteachers provided medication under direct observation at schools. Children who did not attend school on the dosing day were followed up at home to administer medication. Over the course of study follow-up, six participants from the artesunate–amodiaquine group discontinued the study drug on parental request, for reasons based on either family

conflict (n=1, missed third round of medication), mild to moderate adverse events following medication (n=4, missed third round of medication), and or had started antiretroviral medication at the time coinciding with the second dose of medication (n=1, missed rounds 2 and 3 of medication). Decisions to discontinue taking the study drugs were made after thorough discussion with parents, and the children were allowed to continue with routine follow-up visits until the study ended.

Discussion

We found that IPTsc consisting of either dihydroartemisinin–piperaquine or artesunate–amodiaquine delivered three times at 4-month intervals was associated with a small but significant increase in mean haemoglobin concentration and reduced prevalence of malaria parasitaemia at month 12, and reduced incidence of clinical malaria episodes in the first year of intervention among schoolchildren in communities in Tanzania where malaria is endemic. IPTsc is expected to curtail parasite transmission in malaria-endemic communities.[24] The study design allowed an assessment of an interventional period of 1 year followed by another year without intervention to ascertain the risk of rebound effect. In the non-interventional period (from month 8 to month 20—ie, from the last round of IPTsc administration to month 20), the prevalence of malaria parasitaemia was similar to that at baseline. The findings highlight the need for continuous implementation of IPTsc to maintain the benefits in the long term. We hypothesise that, while keeping other malaria control measures intact, routine clearance of parasitaemia with IPTsc could deplete parasites in the transmission cycle in the long term and thereby accelerate the reduction in malaria burden towards elimination. Adverse events recorded in this study were almost all mild and were similar in frequency between the two intervention groups. IPTsc delivery through schoolteachers led to satisfactory compliance and could be useful in future pragmatic implementation.[25] Furthermore, the provision of anthelmintic treatment to all children, regardless of study group, strengthens the evidence that the observed effect on anaemia was mainly caused by a reduction in malaria parasitaemia.

Over the course of IPTsc, the change in haemoglobin showed a varying trend for both drugs, as observed previously.[22] In the dihydroartemisinin–piperaquine group, mean haemoglobin concentration was decreased at month 8 compared with the control group following the second round of treatment; however, at month 12, following the third round of treatment, mean change was 0·5 g/dL higher than that in the control group, despite the mean haemoglobin concentration being similar to the baseline level. The variation could be by coincidence, since haemoglobin was measured almost 4 months after IPTsc treatment. On preliminary analysis in another IPTsc implementation study,[25] we did not see this effect of dihydroartemisinin–piperaquine. However, artemisinin's derivatives have been reported to cause transient reductions in reticulocyte count,[26] and their effects are thus worth exploring. Nevertheless, the overall increase in mean haemoglobin concentration was significant in both drug groups compared with the control group at month 12. A similarly designed study conducted in DR Congo reported a haemoglobin increase compared with the control group of 0·39 g/dL after IPTsc using sulfadoxine–pyrimethamine combined with piperaquine.[22] This effect of IPTsc on mean haemoglobin concentration has also been noted in other studies,[10] suggesting that IPTsc cleared parasites and thereby provided a window for haematological recovery,[6] reducing the prevalence of anaemia. The low but significant effect of IPTsc on anaemia might be explained by the multifactorial causal relationship of anaemia.[22,26,27]

Although most schoolchildren in our study were asymptomatic,[17] the protective effect of IPTsc against clinical malaria and parasitaemia was significant and consistent with previous studies;[10] minor variations compared with previous studies of the protective effect of IPTsc could be explained by differences in transmission periods at the time of assessment. The mean time to first episode of clinical malaria observed in our study was higher than that observed in DR Congo, where mean time to first event was 29 days after sulfadoxine–pyrimethamine and 47 days after sulfadoxine–pyrimethamine plus piperaquine.[22] Given the time to event of 64 days for dihydroartemisinin–piperaquine and 59 days for artesunate–amodiaquine noted in our study, (p 20), these drugs could be strategically applied shortly before the peak of transmission during a season to reduce transmission to other at-risk groups, mainly children younger than 5 years and pregnant women, who tend to have symptomatic malaria and in whom malaria parasitaemia correlates well with that in schoolchildren.[2] This longer protective time would allow for successful pragmatic schedules for implementation, such as administering the drugs once per school term or two to three times in a year (depending on the local number of malaria peaks in a year).[10,28] The transient infection that might occur when the drug's prophylactic effect wanes and the malaria peak is declining could help to maintain naturally acquired immunity[29] and possibly reduce the risk of resistance developing.

Previous studies of IPTsc led to recommendations to use regimens other than artemisinin combination therapies for preventive purposes, because artemisinin combination therapies are used for the treatment of malaria.[6,22] However, antimalarial therapies that do not include artemisinin—such as sulfadoxine–pyrimethamine, amodiaquine, chloroquine, or a combination of such drugs—have faced challenges including development of resistance (eg, sulfadoxine–pyrimethamine)[30] and poor adherence due to adverse events[6,22] limiting their use in IPTsc. Recently, the use of

artemisinin combination therapies for IPTsc that are not used as first-line treatment in that country has been suggested.[10] A drug combination with longer half-life, such as dihydroartemisinin–piperaquine, could provide prolonged protection, as suggested in previous studies.[10] The ideal situation would be the use of a single-dose drug, but none of the currently licensed or marketed drug have this property., Development of a new drug or formulation with such a property would take time, while the need for IPTsc remains eminent. Whichever regimens are used, continuous monitoring of drug resistance molecular markers will be required (eg, using samples from the school malaria parasitological surveys) as an integral part of intervention deployment plans.[3]

IPTsc showed no significant effect on cognitive or psychomotor functions in the current study, which might be due to an insufficient sample size to provide power to detect differences between study groups. Other studies have shown an effect of IPTsc on cognitive and psychomotor function using similar or different testing tools.[6,18] However, previously used tests were not exactly the same as the one used in this study (cognitive score scale of 20 *vs* 40 in our study). Our results showed that psychomotor function was significantly associated with haemoglobin increase (on per protocol analysis), which was in line with other studies.[6,18]

One limitation of our study was the interruption of visit 4 (an important outcome assessment visit) due to the COVID-19 pandemic, when only two schools were visited before closures occurred. This interruption affected the assessment of primary objective on change in haemoglobin after three rounds of IPTsc (at month 12), although the sample size had sufficient power (80%) to detect the differences observed. The overall percentage of missed visits was low at around 19%, and there were no significant differences in baseline characteristics between those lost to follow-up and those who were followed up or in loss to follow-up between study groups, suggesting that the treatment effects were not caused by sampling bias. In addition, the study design including individual randomisation and linear mixed model analysis was robust enough to ascertain the effect of IPTsc on an individual participant level in each study group.

A comparison of participant characteristics between five schools not visited and the two schools visited at month 12 showed some differences (eg, in baseline prevalence of anaemia [57% *vs* 28%], malaria prevalence [26% *vs* 32%], history of malaria in the past month [32% *vs* 22%], and nutritional status; appendix 2 p 4). The individual randomisation with a balanced block approach ensured each school had balanced study groups and the study outcome focused on differences at the individual subject level per group. In addition, after adjusting for factors that differed between study groups (eg, socioeconomic status or weight-for-age *Z* score), the observed effect of IPTsc on change in haemoglobin concentration and malaria prevalence remained essentially the same (appendix 2 pp 13–22). The clinical malaria incidence data were compensatory as most cases were recorded by local health workers even during COVID-19-related school closures. Another limitation is that we were unable to do an extensive battery of cognitive tests for possible comparison with a variety of studies that used different kinds of cognitive tests, and repeated use of the same cognitive test at multiple timepoints meant that improved performance was inevitable across all study groups (ie, participants knew what to expect). We collected data on school academic performance and absenteeism that will be available in a separate publication.

In conclusion, our findings provide additional evidence[10] that implementation of IPTsc should be considered as an important intervention within malaria control programmes, as recommended by WHO's 2023 guidelines for malaria,[28] to reduce the malaria burden in school-aged children in whom malaria parasitaemia is prevalent in most malaria-endemic areas of sub-Saharan Africa, thereby shrinking the reservoir and reducing malaria and anaemia in those communities. For easier implementation, we suggest that IPTsc be sustained and integrated into school-based health programmes (as is currently done for nutrition and mass anthelmintic drug administration), to increase the benefit of anaemia reduction.

Contributors

GMa, VB, JPAL, and J-PVg conceptualised the study. GMa wrote the original draft. FF, GMa, GMt, VB, J-PVg, and SN contributed to data curation, software, visualisation, and validation. GMa, VB, FF, J-PVg, DTRM, SG, and JPAL contributed to project administration, formal analysis, and resources. GMa, VB, DTRM, GMt, RM, EK, JPAL, and J-PVg contributed to investigation and methodology. VB, JPAL, and J-PVg contributed to supervision and funding acquisition. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data will be available from the corresponding author, with approval from the collaborating institutions and a signed data transfer agreement from the National Institute for Medical Research, Tanzania.

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References

1 WHO. World malaria report 2022. Dec 8, 2022. https://www.who.int/publications/i/item/9789240064898 (accessed Dec 31, 2022).

2 Makenga G, Menon S, Baraka V, et al. Prevalence of malaria parasitaemia in school-aged children and pregnant women in endemic settings of sub-Saharan Africa: a systematic review and meta-analysis. *Parasite Epidemiol Control* 2020; **11:** e00188.

3 Chacky F, Runge M, Rumisha SF, et al. Nationwide school malaria parasitaemia survey in public primary schools, the United Republic of Tanzania. *Malar J* 2018; **17:** 452.

4 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:** 1294–309.

5 Walldorf JA, Cohee LM, Coalson JE, et al. School-age children are a reservoir of malaria infection in Malawi. *PLoS One* 2015; **10:** e0134061.

6 Clarke SE, Jukes MC, Njagi JK, et al. Effect of intermittent preventive treatment of malaria on health and education in schoolchildren: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372:** 127–38.

7 Price RN, Simpson JA, Nosten F, et al. Factors contributing to anemia after uncomplicated falciparum malaria. *Am J Trop Med Hyg* 2001; **65:** 614–22.

8 Clarke SE, Rouhani S, Diarra S, et al. Impact of a malaria intervention package in schools on *Plasmodium* infection, anaemia and cognitive function in schoolchildren in Mali: a pragmatic cluster-randomised trial. *BMJ Glob Health* 2017; **2:** e000182.

9 WWARN Gametocyte Study Group. Gametocyte carriage in uncomplicated *Plasmodium falciparum* malaria following treatment with artemisinin combination therapy: a systematic review and meta-analysis of individual patient data. *BMC Med* 2016; **14:** 79.

10 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:** e1499–511.

11 Matangila JR, Mitashi P, Inocêncio da Luz RA, Lutumba PT, Van Geertruyden JP. Efficacy and safety of intermittent preventive treatment for malaria in schoolchildren: a systematic review. *Malar J* 2015; **14:** 450.

12 Okell LC, Reiter LM, Ebbe LS, et al. Emerging implications of policies on malaria treatment: genetic changes in the *Pfmdr-1* gene affecting susceptibility to artemether–lumefantrine and artesunate–amodiaquine in Africa. *BMJ Glob Heal*th 2018: **3:** e000999.

13 Mtove G, Mugasa JP, Messenger LA, et al. The effectiveness of non-pyrethroid insecticide-treated durable wall lining to control malaria in rural Tanzania: study protocol for a two-armed cluster randomized trial. *BMC Public Health* 2016; **16:** 633.

14 Makenga G, Baraka V, Francis F, et al. Effectiveness and safety of intermittent preventive treatment for malaria using either dihydroartemisinin–piperaquine or artesunate–amodiaquine in reducing malaria related morbidities and improving cognitive ability in school-aged children in Tanzania: a study protocol for a controlled randomised trial. *Contemp Clin Trials Commun* 2020; **17:** 100546.

15 Sealed Envelope. Create a blocked randomisation list. https://sealedenvelope.com/simple-randomiser/v1/lists (accessed Feb 3, 2018).

16 Tanzania Ministry of Health. Neglected tropical diseases control program: mass drug administration. https://www.ntdcp.go.tz/activities (accessed Aug 14, 2017).

17 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.

18 Nankabirwa J, Wandera B, Kiwanuka N, Staedke SG, Kamya MR, Brooker SJ. Asymptomatic *Plasmodium* infection and cognition among primary schoolchildren in a high malaria transmission setting in Uganda. *Am J Trop Med Hyg* 2013; **88**: 1102–08.

19 WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011. https://apps.who.int/iris/handle/10665/85839 (accessed Dec 31, 2019).

20 Léger LA, Mercier D, Gadoury C, Lambert J. The multistage 20 metre shuttle run test for aerobic fitness. *J Sports Sci* 1988; **6:** 93–101.

21 Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH. The differential assessment of children's attention: the Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. *J Child Psychol Psychiatry* 2001; **42:** 1065–81.

22 Matangila JR, Doua JY, Mitashi P, da Luz RI, Lutumba P, Van Geertruyden JP. Efficacy and safety of intermittent preventive treatment in schoolchildren with sulfadoxine/pyrimethamine (SP) and SP plus piperaquine in Democratic Republic of the Congo: a randomised controlled trial. *Int J Antimicrob Agents* 2017; **49:** 339–47.

23 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)—a metadata driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42:** 377–81.

24 Staedke SG, Maiteki-Sebuguzi C, Rehman AM, et al. Assessment of community-level effects of intermittent preventive treatment for malaria in schoolchildren in Jinja, Uganda (START-IPT trial): a cluster-randomised trial. *Lancet Glob Health* 2018; **6:** e668–79.

25 Makenga G, Seth MD, Baraka V, et al. Implementation research of a cluster randomized trial evaluating the implementation and effectiveness of intermittent preventive treatment for malaria using dihydroartemisinin-piperaquine on reducing malaria burden in school-aged children in Tanzania: methodology, challenges, and mitigation. *Malar J* 2023; **22:** 7.

26 Cisse B, Cairns M, Faye E, et al. Randomized trial of piperaquine with sulfadoxine-pyrimethamine or dihydroartemisinin for malaria intermittent preventive treatment in children. *PLoS One* 2009; **4:** e7164.

27 Menendez C, Fleming AF, Alonso PL. Malaria-related anaemia. *Parasitol Today* 2000; **16:** 469–76.

28 WHO. WHO guidelines for malaria, 14 March 2023. https://apps.who.int/iris/handle/10665/366432 (accessed Mar 29, 2023).

29 Cowman AF, Healer J, Marapana D, Marsh K. Malaria: biology and disease. *Cell* 2016; **167:** 610–24.

30 Thomsen TT, Ishengoma DS, Mmbando BP, et al. Prevalence of single nucleotide polymorphisms in the Plasmodium falciparum multidrug resistance gene (*Pfmdr-1*) in Korogwe district in Tanzania before and after introduction of artemisinin-based combination therapy. *Am J Trop Med Hyg* 2011; **85:** 979–83.