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Research paper

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

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ABSTRACT

Background: In high transmission settings, up to 70% of school-aged children harbour malaria parasites without showing any clinical symptoms. Thus, epidemiologically, school aged children act as a substantial reservoir for malaria transmission. Asymptomatic *Plasmodium* infections induce inflammation leading to iron deficiency anaemia. Consequently, anaemia retards child growth, predisposes children to other diseases and reduces cognitive potential that could lead to poor academic performance. School aged children become increasingly more vulnerable as compared to those aged less than five years due to delayed acquisition of protective immunity. None of the existing Intermittent Preventive Treatment (IPT) strategies is targeting school-aged children. Here, we describe the study protocol of a clinical trial conducted in north-eastern Tanzania to expand the IPT by assessing the effectiveness and safety of two antimalarial drugs, Dihydroartemisinin-Piperaquine (DP) and Artesunate-Amodiaquine (ASAQ) in preventing malaria related morbidities in school-aged children (IPTsc) living in a high endemic area.

Methods/design: The trial is a phase IIIb, individual randomized, open label, controlled trial enrolling school children aged 5–15 years, who receive either DP or ASAQ or control (no drug), using a "balanced block design" with the "standard of care" arm as reference. The interventional treatments are given three times a year for the first year. A second non-interventional year will assess possible rebound effects. Sample size was estimated to 1602 school children (534 per group) from selected primary schools in an area with high malaria endemicity. Thick and thin blood smears (to measure malaria parasitaemia using microscope) were obtained prior to treatment at baseline, and will be obtained again at month 12 and 20 from all participants. Haemoglobin concentration using a haemoglobinometer (HemoCue AB, Sweden) will be measured four monthly. Finger-prick blood (dried bloodspot-DBS) prepared on Whatman 3 M filter paper, will be used for sub-microscopic malaria parasite detection usingPCR, detect markers of drug resistance (using next generation sequencing (NGS) technology), and malaria serological assays (using enzyme-linked immunosorbent assay, ELISA). To determine the benefit of IPTsc on cognitive and psychomotor ability test of everyday attention for children (TEA-Ch) and a '20 m Shuttle run' respectively, will be conducted at baseline, month 12 and 20. The primary endpoints are change in mean haemoglobin from baseline concentration and reduction in clinical malaria incidence at month 12 and 20 of follow up. Mixed design methods are used to assess the acceptability, cost-effectiveness and feasibility of IPTsc as part of a more comprehensive school children health package. Statistical analysis will be in the form of multilevel modelling, owing to repeated measurements and clustering effect of participants.

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Discussion: Malaria intervention using IPTsc strategy may be integrated in the existing national school health programme. However, there is limited systematic evidence to assess the effectiveness and operational feasibility of this approach. School-aged children are easily accessible in most endemic malaria settings. The evidence from this study will guide the implementation of the strategy to provide complementary approach to reduce malaria related morbidity, anaemia and contribute to the overall burden reduction.
Trial registration: Clinicaltrials.gov: NCT03640403, registered on Aug 21, 2018, prospectively registered. Url https://www.clinicaltrials.gov/ct2/show/NCT03640403?term=NCT03640403&rank=1.

List of abbreviations

ACTs	Artemisinin-based Combination Therapies
AEs	Adverse events
AL	Artemether-Lumefantrine
ASAQ	Artesunate Amodiaquine
ALB	Albendazole
AMA-1	Apical Membrane Antigen 1
$MSP\text{-}1_{19}$	Merozoite Surface Protein 1
CRF	Case report form
CQ	Chloroquine
DBS	Dried blood Spot
DP	Dihydroartemisinin-Piperaquine
DUCE	Dar es Salaam University College of Education
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GHI	Global Health Institute
GMP	Good Manufacturing Practice
Hb	Haemoglobin
IRB	Institutional Review Board
IRS	Indoor Residual Spraying
ISM	Independent Safety Monitor
IPTi	Intermittent Preventive Treatment in infants
IPTp	Intermittent Preventive Treatment in pregnancy
IPTsc	Intermittent Preventive Treatment in school children
ITNs	Insecticide Treated Nets
ITT	Intention to treat
LBW	Low Birth Weight
LLINs	Long-lasting Insecticide Treated Nets
MDA	Mass drug administration
MRCC	Medical Research Coordinating Committee
NSHP	National School Health Programme
NTD	Neglected Tropical Diseases
NIMR	National Institute for Medical Research
NMCP	National Malaria Control Programme
PCR	Polymerase chain reaction
PQ	Piperaquine
Pfkelch13	*Plasmodium falciparum Kelch-13 gene*
Pfcrt	*Plasmodium falciparum chloroquine resistance transporter*
Pfmdr1	*Plasmodium falciparum* multidrug-resistance gene-1
RCT	Randomized controlled trial
mRDT	Malaria Rapid diagnostic test
SAE	Serious adverse event
SDGs	Sustainable Development Goals
SNPs	Single Nucleotide Polymorphisms
SOP	Standard Operating Procedure
SP	Sulfadoxine-Pyrimethamine
STH	Soil Transmitted Helminths
TMDA	Tanzania Medicines and Medical Devices Authority
UA	University of Antwerp
VLIR-UOS	Vlaamse Interuniversitaire Raad–Universitaire Ontwikkelingssamenwerking
WHO	World Health Organization

1. Background and rationale

The WHO malaria report 2019, shows the African region had the largest burden of malaria morbidity, with 213 million cases (93% globally) in 2018 [1]. Though, the report did not categorise malaria burden by age groups, in areas of high transmission (which are mostly in Africa), the main burden of malaria, including nearly all malaria deaths, is in young children [2]. In high transmission settings, up to 70% of school-aged children harbour malaria parasites [3] without showing any clinical symptoms (asymptomatic), thus, acting as a relevant reservoir for malaria transmission [4–7]. A study done in Kenyan school children showed a baseline prevalence of anaemia and *Plasmodium falciparum* infections of 22% and 42% respectively, and were both associated to academic performance [8]. In Muheza, Tanzania, children aged 5–14 years had a *P. falciparum* infection prevalence of 39% that was stable throughout the year [9]. Asymptomatic *Plasmodium* infections induce inflammation leading to iron deficiency anaemia [10]. Consequently, anaemia retards child's growth, predisposes children to other diseases and reduces cognitive potential that could lead to poor academic performance [7,11–14]. If malaria burden decreases due to malaria control activities, school aged children become increasingly more vulnerable as compared to those aged less than five years due to delayed acquisition of protective immunity [2]. In addition, co-morbidities with soil-transmitted helminths (STH), schistosomiasis and malnutrition complicate the problem further as they equally contribute to nutritional deficiencies, anaemia and cognitive impairment [15–17].

Overall, the mainstay for malaria control include the use of insecticide-treated nets (ITNs), indoor residual spraying (IRS), prompt diagnosis and treatment with an effective antimalarial drug ie. Artemisinin combination therapies (ACTs) and intermittent preventive treatment during pregnancy using Sulfadoxine-Pyrimethamine (SP) during pregnancy (IPTp-SP) and Seasonal Malaria Chemoprevention in children under the age of five (SMC) in (sub-) Sahel region [18]. The IPTp as well as SMC have been implemented in several sub-Saharan countries. However, there has been no targeted interventions on school aged children. The importance of malaria burden in school aged children is not well addressed, and consequently adequate support for school-based malaria control interventions is lacking.

A malaria related anaemia and without concurrent fever is highly related to gametocytaemia [19,20]. It has been pointed that reduced haemoglobin (Hb) concentrations are often a consequence of prolonged duration of infections or recurrent malaria episodes [21,22], both of which have been associated with increased gametocyte production [19]. Low Hb concentrations and reticulocytosis directly stimulate gametocyte production [4]. Artemisinins are highly effective against multiple stages of *Plasmodium* targeting both asexual and sexual stages resulting in a substantial parasite biomass reduction [4,23].

The 2015 WHO malaria treatment guideline [24], stipulates that a 3-day course of the artemisinin component of ACTs covers two asexual

cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. It is argued that clearing, otherwise untreated, asymptomatic infections may provide a window 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 [8,25]. A recent review on ACT impact on gametocytes argued that, if transmission is largely driven by asymptomatic individuals (by definition not seeking treatment), then including these asymptomatically infected individuals in treatment campaigns may have a much larger impact on malaria transmission than the choice of ACT for first-line treatment [4]. In addition, some groups working on school children recommended use of ACTs for IPT in endemic settings with high SP resistance [26].

Indeed, a study in Ugandan school children showed Dihydroartemisinin-Piperaquine (DP) was highly effective in eliminating asymptomatic infections when administered as a full course and was superior for preventing new infections compared to SP + Amodiaquine (SP-AQ) [26]. Several other studies conducted in African children for IPTsc strategy using DP alone [3] or in combinations such as SP + Piperaquine (PQ) in the Democratic Republic of Congo [27], DP, SP + AQ and SP + PQ in Senegal [28] and The Gambia [29], have demonstrated the safety and efficacy of these drugs in reducing malaria incidence, anaemia and the feasibility of conducting school based IPT programs. A community based Ghanaian IPT study in under-five children using ASAQ given every 4 months, showed a reduction from 25.0% malaria prevalence at baseline to 3.0% at one year evaluation (protective efficacy 88.0%) and decreased anaemia prevalence from 27.6% to 16.8% [30]. In all these studies, study drugs were effective and safe for IPT in children.

The fact that artemisinin partner drug have noted antagonistic effect on parasite resistance cannot be ignored [31,32]. Suggesting IPTsc using a drug that is a first choice in the treatment guideline may not be a good approach. In this study, we chose DP based on its prophylactic effect and it is an alternative to first line treatment of uncomplicated malaria in Tanzania. We also chose ASAQ which has been noticed to have increased sensitivity in areas where it was banned in the early 2000s as it has been in Tanzania [32]. Nevertheless, the evidence on effective malaria preventive strategies in school aged children still need to be strengthened. Therefore, this study will provide evidence on effective malaria preventive strategies to guide the formulation of policy on targeted malaria control interventions among school aged children.

1.1. Study hypothesis

We hypothesize that, IPTsc with either DP or ASAQ will improve Hb concentration and reduce malaria incidence, with subsequent improvement in cognitive levels in school-aged children. We further hypothesize that, all study drugs (DP and ASAQ) are effective and safe with tolerable minor side effects.

2. Trial objectives

2.1. Primary objectives

The primary objective is to assess the longitudinal impact of a four monthly IPTsc with DP, ASAQ on both anaemia and clinical malaria incidence in school-aged children living in high endemic areas.

2.1.1. Secondary objectives

a. To determine the impact of IPTsc using ASAQ and DP on malaria submicroscopic parasitaemia.
b. To determine the impact of IPTsc using ASAQ and DP on cognitive and psychomotor functions of school-aged children.
c. To determine the impact of IPTsc using ASAQ and DP on the trends of school attendances.
d. To determine the safety of IPTsc using ASAQ and DP among school aged children.
e. To determine the feasibility, cost-effectiveness and acceptability of IPTsc using ASAQ and DP in school children.

2.1.2. Explorative objectives

a. To determine the impact of IPTsc on acquisition of immunity to malaria in school-aged children.
b. To determine the impact of IPTsc with ASAQ and DP on drug resistance.
c. To estimate the prevalence of STH, schistosomiasis, co-infections of malaria-STH among school-aged children.

3. Methods/design

3.1. General study design

This is a randomized, controlled, open label study assessing the effectiveness and safety of two antimalarial drug-combinations for IPTsc, namely DP and ASAQ by a 3-arm trial using a “balanced block design” with the “standard of care” arm as reference. Randomisation was done using available online randomisation service [33], where block size of six was assigned to ensure equal representation of each study arm. This setup, allowed the study team to conduct recruitment within a period of one month (at baseline). During enrolment, every six pupils from the same class used the same randomisation block to ensure balanced allocation per school and within class. Eligible school children, were randomized to receive either full course of DP or ASAQ or control (no drug), they will be followed up for a period of 20 months categorised in two years. The interventional treatments are given at four months intervals for the first year, a second non-interventional year will assess possible rebound effects (see Fig. 1). Study arms are distributed to allow a head-to-head comparison and the establishment of the treatment’s relative value according to a series of outcomes. All study-arms receive the recommended malaria control interventions e.g. bed nets and early diagnosis and care, which, also takes control of any confounding effect from ongoing interventions. In combination, other school health control interventions (i.e. against schistosomiasis and STH) are incorporated. Mixed design methods are used to assess the acceptability, cost-effectiveness and feasibility of this IPTsc as part of a more comprehensive school children health package. This approach has the advantage of testing two treatment options at the same time, maximizing the use of resources, and most likely, this will provide identification of antimalarial suitable for IPTsc.

3.2. Study area and school selection

The study is conducted in Muheza District, Tanga, North-eastern Tanzania (Fig. 2), where, malaria transmission occurs throughout the year with two seasonal peaks following the long rainy season from July to August and the short rainy season from December to January [9]. Malariometric surveys conducted in 2014 at Muheza showed mean malaria prevalence of 22% and 25% after the short and long rains, respectively, and was significantly higher among children aged 5–14 years old, compared to those <5 years old (38% vs. 18% and 39% vs. 34% after the short and long rains, respectively) [9]. It was from this Muheza data, that schools located in villages with high malaria prevalence were selected in descending order until the targeted sample size was reached. The existing pillars for malaria control in the area includes use of Long Lasting Insecticides Nets (LLINs) and prompt diagnosis and treatment with ACTs (mainly artemether-lumefantrine, AL) as the first line treatment for uncomplicated *falciparum* malaria [34]. Intervention on pregnant women (IPTp-SP) is implemented as a policy countrywide

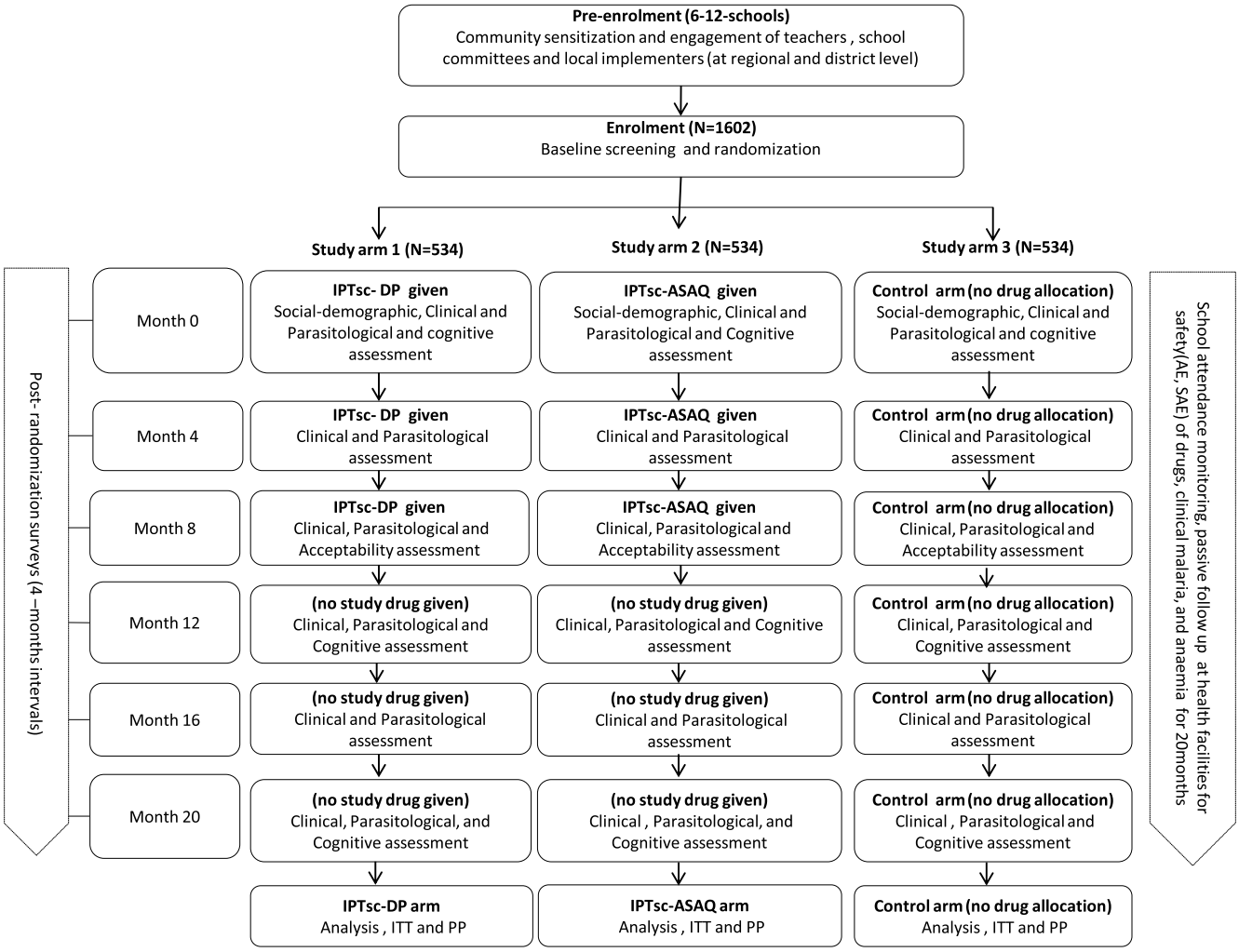

Fig. 1. Trial flow chart.
IPTsc = intermittent preventive treatment in school-aged children; DP = dihydroartemisinin-piperaquine; ASAQ = Artesunate Amodiaquine; AE = adverse event; SAE = serious adverse event; ITT = intention-to-treat analysis; PP = per-protocol analysis.

as per the WHO recommendations and national malaria treatment gudelines. However, evidence suggest that the strategy is seriously compromised due to the alarming level of high-grade SP resistance in some regions and especially in north Eastern Tanzania [35]. The high grade SP resistance harbouring K540E and A581G mutation (proxy for the sextuple mutants) in the *Pfdhps* gene have been described in the area [36].

Current primary school enrolment at Muheza District is about 98% and the number of pupils ranges from 150 to 1500 per school. As of February 2019, there were about 111 registered primary schools with about 90,160 enrolled pupils. In this study, the participants are recruited from seven selected primary schools located in villages with high malaria prevalence in Muheza district [9]. Study team make regular visits at selected schools where engagement with the Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC), the Ministry of Education Science and Technology and the President's Office Regional Administration and Local Government (PO-RALG) has been established. In addition, several other community-based studies have been conducted by the NIMR in Muheza and have established good cooperation with the local community leaders and community members. In this study, from each of the involved village; community health workers, school health teachers, local health facility health workers and village administrators are involved during surveys and in continued follow-up to capture adverse events and school absenteeism.

3.3. Randomisation

Randomisation was done using available online randomisation service [33], where block size of six was assigned to ensure equal representation of each study arm. The data manager generated the list of 300 blocks of 6 (i.e.1800 allocations) and prepared the blocks in the envelopes that were provided to a study nurse. During enrolment, every six pupils from the same class used the same randomisation block to ensure balanced allocation per school and within class. Pupils deemed eligible by the study clinicians would pass through the study nurse for randomisation. Since the study is open label, the nurse would follow the list as provided by the data manager to openly allocate the pupils in respective study groups. The nurse would document the randomisation number and study group assigned on each pupils' case report form (CRF). The allocation paper from the envelope would also be pinned/-stapled on the CRF's randomisation section. The number of blocks assigned per school were determined by the number of pupils who are class 5 or below who would possibly be recruited. Recruitment was done in a successive pattern, where schools were assigned numbers from the first to the last to be recruited i.e., school 1 (S1), school 2 (S2), school 3 (S3) etc. Then, each school received its randomisation blocks in a successive order, i.e. S1 received block number 1–35 because it had 210 possible eligible pupils (i.e.35x6), S2 received block number 36–80 because it had around 270 possible eligible pupils and so forth for S3, S4,

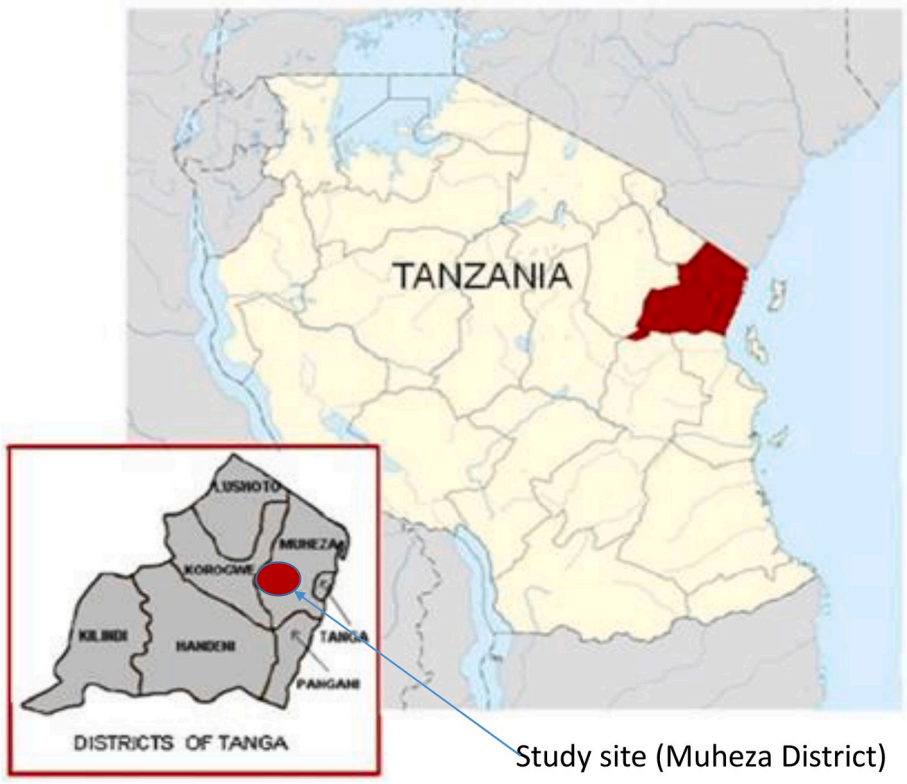

Fig. 2. A map of Tanzania showing study site location.

S5, S6, and S7. This allowed the team to allocate time to recruit those who missed in the previous school but following their respective blocks assigned in that particular school. Thus, randomisation blocks were never mixed between schools. Eligible school children, were randomized to receive either full course of DP or ASAQ or control (no drug).

3.4. Sensitisation and recruitment

At different stages of study implementation, the study team liaised with the local government officials mainly the District Medical Officer (DMO), the Council of Health Management Team (CHMT), malaria and NTDs program officers, District Education Officer, Head of selected primary schools, school committees, village leadership and village health workers including other community stakeholders such as religious leaders and later parents or guardians of children in the selected schools for study briefing to attain support and local community engagement for the study.

We aimed to recruit a total of 1602 children (534 per study arm) aged 5–15 years who were class 5 or below accumulated from 6 to 12 primary schools selected. In each school all children of class 5 or below were regarded as possible participants. We excluded those in class 6 or 7 due to the fact that they will graduate before the study ends. During sensitisation meetings that were held at schools and included all parents or guardians and village leaders (typically a school meeting), interested parents or guardians were consented on their children participation to the study. Children were enrolled after obtaining a written consent from respective parents and or guardian. Full-enrolment was determined after all inclusion criteria have been met. Parents or guardian and pupils were informed of their right to withdraw from the study at any time. In order to avoid reporting bias or missing information, baseline data on social demographics and well-being of school children were obtained from parents or guardians who have signed consent, at this stage home visit was necessary for global positioning system (GPS) satellite location data and verification of social demographic data with regard to household characteristics. In case a parent or guardian missed a briefing meeting, he/she was followed at home for briefing and consent processes.

3.5. Selection and withdraw criteria

3.5.1. Inclusion criteria

The following inclusion criteria are adhered:

a. Male and female primary school children in a selected school
b. Includes parental/guardian informed consent.
c. Assent by primary school children aged 11 years and above.
d. Aged 5–15 years at the baseline assessment.
e. Currently, lives within the pre-defined catchment area of Muheza District.
f. Will remain within the same area throughout the study period (preferably pupils of class five and below).

3.5.2. Exclusion criteria

Participants with at least one of the following criteria are excluded:

a. Pupils of class/grade 6 or 7
b. Currently enrolled in another study or participated in another investigational drug study within the last 30 days.
c. Known to have heart disease or a known cardiac ailment.
d. Reports known hypersensitivity to the study drugs or any sulphonamides.
e. Not willing to undergo all study procedures including physical examination and to provide blood samples as per this study protocol.
f. Having clinical features of severe anaemia
g. Has apparent severe infection or any condition that requires hospitalization
h. Illness or conditions like haematologic, cardiac, renal, hepatic diseases which in the judgement of the investigator would subject the

participant at undue risk or interfere with the results of the study, including known G6PD deficiency and sickle cell traits.

i. Body weight <14 kg

3.5.3. Withdrawal criteria

Study withdrawal is an event where a participant who is randomised to a treatment group but does not complete the study or study procedures including medication. If a participant gives informed consent and then does not enter the study, is classified as a screen failure. If a participant shifts to another school that is not involved in the study, s/he is regarded as lost to follow up. Every effort is made to follow-up participants who are withdrawn due to drug-related adverse events in order to determine the final outcome of the adverse event. Participants may choose to withdraw or be asked to withdraw for any one of the following reasons: Withdrawal of consent (at any stage), severe adverse event related to study drug, protocol deviation (including non-compliance), lost to follow-up, termination by sponsor and discretion of the investigator.

3.6. IPTsc intervention, drug administration and accountability

3.6.1. Investigational drugs

3.6.1.1. Dihydroartemisinin Piperaquine (DP). A fixed-dose combination (FDC) of piperaquine with dihydroartemisinin was approved by the European Medicines Agency (EMA), and is also registered by the Tanzania Medicines and Medical Devices Authority (TMDA). The Tanzania's national malaria treatment and diagnostic guideline [34] considers DP as an alternative to first line ACT (i.e. AL) in treatment for uncomplicated malaria. This drug is safe and efficacious at 60–73.9 mg/kg dose in 3 daily doses against uncomplicated *P. falciparum* malaria [37,38]. The ED90 of PQ at 1.68 ± 0.21 mg/kg/day for *P. berghei* K-173, CT100 of 42h and has a long elimination half-life [39]. In this study, DP will be dosed using weight-based guidelines targeting a total dose of 6.4 mg/kg dihydroartemisinin and 51.2 mg/kg PQ [3] and will be given as per manufacturer's instruction. The DP drug (D-Artepp) manufactured by Guilin Pharmaceutical Co Ltd from China was donated for this study by Guilin pharmaceuticals Tanzania limited.

3.6.1.2. Artesunate Amodiaquine (ASAQ). This drug is indicated for treatment of uncomplicated malaria [34]. A fixed dose combination is available and results in better treatment efficacy than loose tablets. Artesunate is a semi-synthetic derivative of artemisinin that is water-soluble quickly adsorbed orally, the highest concentration in blood is achieved within 1 h following an oral intake and the half-life is between 20 and 72 [40]. Artesunate, like other artemisinin derivatives, kills all erythrocytic stages of malaria parasites, including the ring stages and early schizonts, as well as the gametocytes responsible for continuing transmission, although it has only partial activity against the mature stages (stage V) gametocytes [24]. Amodiaquine is readily absorbed from the gastrointestinal tract and rapidly converted by the cytochrome P450 (CYP) enzyme CYP2C8 into *N*-desethylamodiaquine (DEAQ), which is the main metabolite of amodiaquine (AQ). While AQ is a prodrug which is rapidly eliminated, the elimination of DEAQ is slower, with a terminal half-life of 4–10 days [24]. Children will receive 10 mg/kg body weight of amodiaquine (AQ) and 4 mg/kg of artesunate (AS) daily (given as a single dose) over three days [30,41]. The WHO prequalified ASAQ (ASAQ Winthrop®) drug manufactured by Sanofi Pharmaceuticals were procured from HighChem Pharmaceuticals, a Sanofi agent/distributor in Kenya.

3.6.1.3. Treatment administration and assessment of compliance. Pupils who meet all inclusion criteria, are randomised to allocate them into three study groups and hence receive allocated study drugs. Children are observed for 30 min after ingesting the study drug. If a child vomits within this time period, he/she is given another course only to repeat once and the information is documented on the electronic CRF. If a child vomits the study drug for the second time, he or she is withdrawn from receiving the study drug. The study drugs are administered basing on participant's weight following manufacturer's instruction (package insert/leaflet). Both DP and ASAQ have a three days full dose course (administered once per day). Study nurses are responsible for dispensing the first day dose, while doing this they also train school health teachers for administration of the same drugs and documentation on accountability logs. School health teachers would administer subsequent doses (day 2 and 3) to participants receiving study drugs, while study nurses would supervise them. This will happen in all three rounds planned for IPTsc intervention. This ensures that all IPTsc study drugs are directly observed and compliance assessed, and a capacity is built among teachers. In case the IPTsc programme becomes a national policy, teachers would be key people to administer the drugs as it happens for MDA of NTDs that are delivered through schools. In all three days of drug administration, we also provide lunch to all pupils in the school regardless of their recruitment statuses. Lunch is usually composed of rice and beans, a staple food in Tanzania.

3.6.1.4. Medicines accountability. Study drugs are stored at adequate security and environment as described by the manufacturer. At the pharmacy temperature is monitored and there is a drug accountability form, where the pharmacist records drugs received (shipped in) from suppliers and also drugs given out to field nurses for a particular field activity. The field nurses account for drugs they dispense to eligible participants by filling a special drug dispensing log, following the randomisation list. The drug dispensing log records participants' study ID, participants' initials, and date dispensed, dose/number of tablets given, comments on whether a participant vomited or not. Appropriate standard operating procedures (SOPs) are adhered both by the pharmacist and the nurse dispensing drugs to study participants. The drug accountability form and the drug dispensing log will be used for drug reconciliation for accountability of all drugs received, dispensed or destroyed in case of expiration. All study drugs either received in from suppliers or sent to the field are verified by the investigator or designee.

3.6.2. Non-investigational drugs

3.6.2.1. Albendazole. An oral 400 mg treatment will be given at month 0, and 12 following the WHO guideline and the national NTD programme. The drug is provided after stool and urine samples have been collected at baseline and at month 12. All enrolled children receive the drug irrespective of their study group and or stool/urine analysis results. A single tablet of 400 mg is administered orally under direct observation. Children are required to chew it. In case one spits it another tablet is provided. Both study nurses and school health teachers administer the drugs to enrolled participants. Since the timing for annual MDA by NTD national-wise could overlap with that of the study; the study team works closely in liaison with the district NTD coordinator, to ensure schools in the study area are not provided the drug twice (i.e. as annual MDA by NTD and by study team) or before the team has collected stool and urine samples.

3.6.2.2. Praziquantel. This will be given at 40 mg/kg orally to children found with schistosomiasis infection. Basing on body weight, praziquantel will be provided as per study clinician's prescription.

3.6.3. Concomitant treatments

During enrolment and follow up, the administration of paracetamol (acetaminophen) is allowed for participants found with fever (>37.5 °C). This together with any other medication provided for treatment during visits, or taken by the participant during the trial period, are all recorded on the appropriate section of the CRF and adverse event (AE)

form. Drugs with antimalarial activity (such as co-trimoxazole, macrolides, tetracycline or doxycycline) are also reported as concomitant.

3.7. Routine follow up visits

The study has 6 visits for surveys that are done after every 4 months where the first three visits includes study drug administration, while the successive visits are for assessment of rebound effect (Table 1). During these surveys we collect clinical samples as scheduled on Table 1. We also conduct monthly visits to schools and local health facilities to collect information on school attendance and reported illnesses during that month. Enrolled children were given special identity cards that show scheduled follow up visit to be conducted within schools in collaboration with teachers and local community health workers (CHW). In each school, the study team works closely with the Head teacher, 2 school health teachers and 2 CHWs. If a participant misses school on the day of follow up visit, the study team will do home visit for such a participant. During or in between follow up visits, teachers in each school are encouraged to contact the study team via phone whenever a study participant is absent or is sick. Any sick or unwell child together with his/her parent or guardian are advised to visit a nearby health facility with notification to the study team.

Table 1
Follow up chart of study participants in IPTsc study at Muheza district (Tanzania).

Time points in months	Baseline	4	8	12	16	20
Actual time lines	Mar/ Apr 2019	Aug 2019	*Jan 2020	Apr 2020	Aug 2020	Nov/ Dec 2020
Eligibility screen	X					
Informed consent	X					
Social-economic and demographic	X					
History (symptoms)	X	X	X	X	X	X
Clinical physical examination	X	X	X	X	X	X
Randomize to study groups	X					
Blood slide for malaria parasites	X			X		X
Haemoglobin	X	X	X	X	X	X
Stool and urine samples	X			X		X
Dried blood spot (DBS) from finger prick	X	X	X	X	X	X
PCR for submicroscopic malaria infection[a]	X	x	x	X	X	X
DP and ASAQ drug resistance makers[a]	X			X		X
Serology for malaria[a]	X			X		X
School attendance monitoring	X	X	X	X	X	X
School performance	X			X		X
Cognitive and psychomotor assessment	X			X		X
Study drugs administration as randomised	X	X	X			
Adherence assessment	X	X	X			
Cost effectiveness and acceptability assessment			X			
Data review and quality check	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
STH treatment	X			X		

[a] processed from DBS samples, * Due to school holiday in December 2019.

3.8. Illness records and attendance tracking

Health workers at the health facilities in the study area are involved in the study for documenting events found to sick participants who happen to have attended at respective health facilities. All children presenting with any symptom at a health facility are checked for malaria using malaria rapid diagnostic test (mRDT). Case report forms with incentives are presented to health workers for this purpose. In addition, the study clinician would make weekly calls to each school confirming participant's attendance and remind teachers to document such occasion in a special attendance form. For children who missed school on any day of that week, the CHW is contacted to do a home visit to find out reasons for missing school if it was not reported at school. In case the reason may be a child was sick, information of the child's sickness and management thereof will be documented by the CHW in collaboration with the study clinician and the health workers at the health facility in which the child was attended.

During scheduled study visits, all children found with fever (temperature $\geq$37.5 °C) or report history of fever in the past 48 hours, regardless of study arm are tested for malaria using mRDT and get treated according to national standard treatment guideline (i.e. given AL if mRDT positive). However, if one is in the intervention arm (DP or ASAQ), s/he receives the respective study drug as long as one is diagnosed with non-severe malaria.

It should also be known that, not all villages in the study area have a health facility, in this case the CHW have been trained for early diagnosis and treatment of malaria using mRDT. They have been trained to dispense AL which is the first line treatment of uncomplicated malaria in Tanzania. If the illness is severe or is not malaria, they provide referral to a hospital facility for further management, where the study team will reimburse the treatment cost to parents or guardians. The study team does routine check up on quality of care and supplies provision. The CHW involved in the study are experienced on use of mRDT and malaria treatment as per national guideline, they have been trained not just in this trial but also other studies that NIMR has conducted in the study area in the past.

At the end of the study or at month 12 all documented cases will be pulled for malaria incidence calculation, this will be compared per study group in the analysis.

3.9. Strategies for retention

Although by nature of this study, we expect retention rate to be high. However, during enrolment, potential participants were asked of their availability in the study area for the entire study duration. In addition, children in their last years of school i.e. those in class six and seven were not recruited. The study team ensured participants have understood the informed consent and adhere to study procedures (Table 1). During follow up, school teachers and CHWs are incentivised in terms of communication allowance to help capture data on absentees and those who are sick in a real-time manner. Since the population is dynamic, in case, it happens that a participant shifts to another school not included in the study, he or she is considered a lost to follow up. However, in case it happens one has shifted to another school involved in the study, subsequent follow up will continue and his/her data will be included for analysis.

3.10. Safety assessment

Adverse events are collected from the time a participant has been enrolled to the study and throughout the duration of the study or until withdrawal. Study clinicians and or nurses ask participants a non-leading question in order to detect any AE encountered, this is documented in the CRF. The nature of each experience, date and time

(whenever appropriate) of onset, duration, severity are recorded. Serious adverse events (SAE) or AEs not previously documented in the study will be recorded in the adverse experience section of the electronic CRF. The investigator reviews all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The severity and relationship of an event to treatment is established by using clinical judgement. The intensity of each AE and SAE recorded in the CRF is assigned to one of the following categories: Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities. Severe**:** An event that prevents normal everyday activities. Details of any corrective treatment will be recorded on the appropriate pages of electronic CRF.

Previously assessed AEs and designated as 'continuing' are tracked by the study clinician through regular phone calls and at weekly interval to the parent or caregiver or class teacher or CHW in order to review and get event's outcome prior to next visit. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the AE will be updated on the site AE tracker. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals or facilities. If an adverse experience changes in frequency or severity during a study period, a new record of the experience is started.

All AEs reported or detected will be summarised and accompany reports prepared for the sponsor and regulatory authorities. Separately, and per SOPs and or regulation, NIMR will provide the TMDA and MRCC with biannual reports of AEs observed incorporated on the six monthly reports. In contrast, SAEs will be reported to the sponsor immediately (within 24 h) from the time an investigator becomes aware. The SAE form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to the ethical and regulatory authorities and the sponsor without delay. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Investigators, Sponsor and the Authorities (TMDA and NIMR-MRCC) of the event and completing the SAE form. The form will be updated when additional information is received. E-mails will be used to transmit the SAE form followed by e-mail or telephone confirmation of receipt. All SAEs will be reported to local ethical and regulatory authorities (NIMR-MRCC and TMDA) within the time frame required, normally within 24 h for fatal ones, and within 14 days for non-fatal SAEs/SUSAR.

3.11. Cognitive and psychomotor assessments

To determine the benefit of IPTsc in school children on cognitive and psychomotor ability, selected children were assessed at baseline, and will be assessed again at month 12 and 20 for psychomotor, and cognitive impairments to determine risk factors and benefit of IPTsc interventions in averting the impairments. At baseline, we collected data on child's school performance for the past one year; this will be compared with that at month 12 and 20 of the study follow-up. For cognitive ability test, we adopted the method used by Clarke *et al.,* in 2008 and 2017 on studies conducted in Kenya [8] and Mali [7], respectively. These were also used elsewhere [42] including Tanzania [16]. We, therefore, selected enrolled pupils from class 4 and 5, who we presume are old enough to understand the cognitive test instruction. We evaluated sustained attention using two code transmission tasks, adapted from the TEA-Ch (Test of Everyday Attention for Children) battery by Manly T. *et al.* [43,44] as described by Clarke *et al.*, 2017. Tests involved listening to a pre-recorded list of digits read aloud at the speed of one per second. Children were required to listen out a 'code' [two consecutive occurrences of the number 5] and to write down the number (single-digit test) or two numbers (double-digit test) which immediately preceded the code. Cognitive evaluation was assessed at baseline and will be done again at month 12. Physical fitness was assessed using the 20mShuttle Run Test (20mSRT). During this test, children ran continuously between two lines apart turning when signalled to do so by recorded beeps and a "shuttle" was defined as a run between one line to another. The 20mSRT has 20 levels [16,45]. This will also be conducted again at month 12 and 20 of follow up.

3.12. Implementation research

To determine acceptability of the study strategy, including community and frontline caregivers' perceptions on the recommended drug combination usage. Qualitative research will be conducted at month 8 following the final dose of IPTsc. Respondents will include study participants/parents, teachers, other school staff, study personnel, policymakers'/implementation specialists at the ministries responsible for health and education. Two focussed group discussions (FGD) per school (one for boys and one for girls) will be conducted to pupils receiving the intervention (about 10 randomly selected pupils distributed equally per intervention arm). Also in each school, in-depth interviews (IDI) will be conducted to two school health teachers and four randomly selected parents (two per study intervention arm). Also IDI will be conducted purposefully to district officials responsible for malaria, NTD, school health programs and other stakeholders. Questionnaire and interview topics will be adapted to the respondent type and include: sociodemographic details, experiences of IPT, perceptions of IPT, ideas about malaria and malaria prevention, potential bottlenecks in implementation of the IPT strategy following relevant models/framework [46–49]. Data collection tools will be pre-tested with a number of respondents by the investigators and research assistant together to ensure comprehension and appropriateness. With the consent of participants, in-depth interviews and focus group discussions will be audio-recorded and transcribed verbatim (10% checked independently for accuracy). The Investigator and research assistant will also record observations of the administration of IPTsc as field notes.

3.13. Laboratory methods

3.13.1. General overview

All samples including those taken at baseline will be processed and then archived in a central laboratory located at NIMR Tanga centre. Samples are labelled without revealing the randomisation group of a participant. Therefore, laboratory technicians are blinded on drug allocation of the participants. Thick and thin blood smears were obtained prior to treatment at baseline, and will be obtained again at month 12 and 20 from all participants. Malaria parasitaemia will be detected from blood slide after double reading by expert microscopists to verify the presence of P. *falciparum* and calculate the parasite density. Haemoglobin concentration was measured at recruitment and will be measured again during scheduled follow up visits using a haemoglobinometer (HemoCue AB, Sweden). Finger-prick blood (dried bloodspot-DBS) samples were collected at baseline and will be collected at every visit, being prepared on Whatman 3 M filter paper, air-dried and stored in plastic bags containing desiccant and archived at −20 freezer. These DBS samples will be used for sub microscopic parasite detection (by PCR), detect markers of drug resistance, malaria serological assays and future host-parasite genetic studies.

3.13.2. Blood slides for malaria parasite

Malaria parasitaemia will be checked prior to treatment at every visit in all participants. Thick and thin blood smears will be obtained to verify the presence of *P. falciparum* and to calculate the parasite density. Thick and thin blood films will be prepared, dried and stained with Giemsa stain according to SOPs. Parasite density will be calculated by counting

the number of asexual parasites per 200 leukocytes in the thick blood film, based on an assumed WBC of 8000/μl by light microscopy at 1000× magnification. One hundred high-powered fields (HPF) will be examined (independent of presence or absence of asexual parasite stages). The parasite density per school will be calculated using the following formula:

$$\text{Parasite density}/\mu\text{l} = \frac{\text{Number of parasites counted} \times 8,000}{\text{Number of leukocytes counted}}$$

Two slides will be prepared for each participant, one will be read by two technicians and kept in the archives and a second will be retained for external quality control. The blades thick and thin smears reading will be performed by two independent technicians. If the discrepancy is greater than 15%, a technician will perform the third reading to decide between the two. A blood smear will be considered negative if no parasite is observed after travelling 100 microscopic fields.

3.13.3. Haemoglobin concentration

Haemoglobin concentration will be measured at recruitment and during scheduled follow up visits using a haemoglobinometer (HemoCue AB, Sweden).

3.13.4. Stool and urine samples

Stool and urine samples were collected at Month 0 and will be collected at 12 and 20 months. A stool sample will be used to determine prevalence (defined as adult worms or eggs) of STH and *S. mansoni* infection in school-aged children determined by duplicate Kato-Katz thick smears technique as reported elsewhere [50,51]. Stool samples will be labelled and stored in a refrigerator at 4 °C after collection until examined in the laboratory. Each child will be given a urine container and asked to collect 10 mL of the urine specimens. The samples will be visually examined for the presence of blood (macrohaematuria) followed by laboratory examination for schistosomiasis infection (*S. haematobium*) and presence of eggs as previously reported [50,51].

In this procedure, one stool and one urine samples will be collected. From the stool specimen, two slides of 25 mg will be processed according to duplicate Kato-Katz thick smears technique. The urine sample will be read on strip for search of microscopic haematuria. From each urine sample with (macroscopic or microscopic) haematuria, 2 slides will be made after filtration of 10 ml on filters. Each slide will be checked for the presence of eggs by microscopy and the number of eggs per gram (epg) in stool per 10 ml (ep10mL) urine will be determined.

3.13.5. Sample archiving

All samples will be processed in the laboratory following respective SOP and will then be archived in a central laboratory located at NIMR, Tanga centre.

3.13.6. Molecular analyses on sub-microscopic infection, drug resistance and serology

The occurrence of *P. falciparum* qPCR-positives will be measured in finger-prick blood samples from a random subset of school children at enrolment with an estimate of 22.5% (n = 120 from each study arm, in total n = 360). A similar random sub-sample at month 12 and 20 will be examined (n = 1080). DNA will be extracted from filter paper using the QIAamp® DNA Blood Mini Kit (QIAGEN) as per manufacturer's recommendation. A highly sensitive method based on *Plasmodium* species specific real time qPCR will be used to examine the samples [45,52].

All samples that are qPCR positive for *P. falciparum* at any given sampling point (month 0, 12 and 20) will be analysed for relevant genetic markers of drug resistance. All qPCR positive samples (depending on drug arm) will be examined for SNPs of relevance for Piperaquine (*Pfmdr1*), AQ (*Pfmdr1* and *Pfcrt*) and artemisinin resistance (*Pfkelch 13*) gene mutations. Candidate molecular markers for PQ resistance; *Plasmepsin 2-3 copy numbers* will be analysed as reported elsewhere [53,54], plus any markers identified in the literature in the course of the project will also be examined. The detection of the targeted drug resistant genes will be carried out using a high-throughput next-generation sequencing (NGS) based on Illumina® platform [55]. After amplifying DNA sequences using multiplex PCRs, gene fragments will be sequenced using the Illumina Miseq® platform and each gene sequence will be indexed according to time and sampling site of origin using the platform. This will allow for simultaneous sequencing of at least 1000 samples in a Miseq assay, which will reduce workload and related costs.

Antibody response to *P. falciparum* will be determined by ELISA using eluted dried blood from filter paper as described by Idris *et al.* [56] and Coran *et al.* [57]. A 3 mm disk will be punched from each dried blood spot and serum will be eluted in reconstitution buffer in 0.5 ml deep well plates (Corning Costar, PA, USA). The reconstituted blood spot solution, equivalent to a 1/200 dilution of serum, will be stored at 4 °C until used for antibody test. All sera will be tested for IgG antibodies by indirect quantitative ELISA to two recombinant blood-stage *P. falciparum* malaria antigens namely *apical membrane antigen-1* (*AMA-1*) and *merozoite surface protein-1 (MSP-1$_{19}$)*. Methods by Idris *et al.* [56] will be followed to further process and analyse serological assays.

3.14. Data management

This research generates qualitative and quantitative data (e.g. sociodemographic, clinical evaluation and laboratory data). Data is collected and managed through Research Electronic Data Capture software package (REDCap) which is hosted by the University of Antwerp. REDCap is a mature, secure web application for building and managing online surveys and databases housed by Vanderbilt University [58]. Android or iOS tablets are used to enable data collection offline or in remote places where internet connection is not possible. Hence, the electronic CRF from the REDCap database is uploaded to an electronic mobile device that is used to collect data and later uploaded to the main study on the central server located at the University of Antwerp (UA). Data from laboratory measurements are entered from the paper form into the tablet later and also uploaded to the server. Before data collection, measures such as piloting, pretesting and validation of tools were done to secure high data quality. In addition, REDCap provides data quality features that can be used to check for discrepancies in the data collected.

During the trial, all paper-based forms are kept in a locked cabinet with access restricted to authorized study staff. Computerized data system is locked with password only granted to authorized study staff. The computer servers are protected by a firewall against malware. The servers are backed up on a quasi-permanent base on a second server which ensures that all the data are secured in case of any unforeseen accident.

Measures are undertaken to ensure that all personal data collected during the study are appropriately protected. The collection of personal information is restricted to only the objectives of the trial, and only data relevant for the execution of the trial and interpretation of data is collected. Collected information is kept for a minimal time period, which is regulated by national or international laws. All personal data collected during the study is kept confidential.

The data transfer agreement has been signed by collaborating institutions and obtained approval from NIMR-MRCC, Tanzania.

3.15. Sample size calculation

Basing on the primary outcome, since change of Hb will be assessed per individual participant, we calculated sample size using a paired T-test, where, a sample size of 1602 participants (534 per study arm) was suitable to detect a change in Hb level of 0.2 g/dL (effect size based on previous study [27]), at a type one error of 0.05 ($z_{1-\alpha} = 1.96$), power of 90% ($z_{\beta} = 1.282$), assuming a standard deviation (SD) of 1.25 g/dL and a loss to follow-up of 30%. This was calculated using formula by Noordzij

et al. [59] and an online calculator [60].

Basing on a previous study in the same area [9], primary schools were selected from villages with high malaria prevalence. In case a selected village had primary schools with less number of eligible pupils, then more schools in that village/area were added. Participants were individually randomized in blocks of six to equally allocate them into three study groups.

Again a sample size of 922 participants was deemed sufficient to detect 88 events with equal proportion allocation in three study groups ($\pi_{1=}\pi_2 = 0.5$), using a power of 90% ($z_\beta = 1.282$), type one error of 0.05 ($z_{\alpha/2} = 1.96$), assuming intervention will be able to reduce malaria incidence rate by half [Hazard Ratio (HR) of 0.5] and 30% loss to follow-up. The probability of events being 0.2, determined at an incidence rate of 3.0 at site [9] [i.e. $S_1 = 0.3$ and $S_2 = 0.15$]. This sample size was calculated using the formula by Weaver *et al.* [61].

3.16. Outcome measures

3.16.1. Primary endpoints

The primary endpoints are grouped as follows:

1. Impact of IPTsc on Anaemia:
   a. change from baseline in mean Hb concentration at month 12 and 20 of follow-up.
   b. and prevalence of anaemia at baseline and at month 12 and 20 of follow up.
2. Impact of IPTsc on clinical malaria incidence:
   a. the clinical malaria incidence from month 0 till months 12 and 20 of follow up. This will be measured from the number of cases (malaria illness) accrued from baseline to month 12 and 20 of follow up.

3.16.2. Secondary endpoints

a. Prevalence of asymptomatic malaria infections at month 0, 12 and 20 of follow up.
b. Prevalence of PCR confirmed sub-microscopic parasitaemia at months 0, 12 and 20 of follow up.
c. Improvement in the cognitive and psychomotor test scores evaluated at baseline and at month 12.
d. Improvement in school attendance, at month 12 and 20 compared to baseline.
e. Proportion of participants completing dose of given study drugs.
f. Implementation cost of delivering IPTsc using DP and ASAQ in school aged children
g. Relative risk (RR), for all adverse events categorised to severity at month 12 and 20.

3.16.3. Explorative endpoints

a. Prevalence of STH, schistosomiasis at baseline and month 12 of follow up.
b. Proportion of school children with malnutrition at month 0, 12 and 20 through WHO's BMI z-score
c. Prevalence of validated common *P. falciparum* polymorphisms known to be associated with drug sensitivity at baseline, at months 12 and 20.
d. Proportion of children seropositive for *P. falciparum apical membrane antigen (AMA-1)* and *merozoite surface protein 1* ($MSP\text{-}1_{19}$) at baseline, at month 12 and 20.
e. Change in serum antibody responses to *P. falciparum AMA-1* and $MSP\text{-}1_{19}$ at baseline, at month 12 and 20.

3.17. Quality assurance

The study is done in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines (ICH-GCP). The quality assurance of records and data are guaranteed. The study team were trained about the study protocol prior to start of the trial. The study clinicians and nurses complete CRF at each school visit. The investigators or designee carry out 100% Source Data Verification during the school visits and on follow-up to guarantee the best conduct of the study. Accuracy of the data, is ensured by contra-checking a completed CRF by another investigator or designee. The consistence of data is checked by the clinician, who, cross-checks the reports of the school teachers and of parents/guardians, and the medical records documented at the health facility. The investigators, have frequent contacts with the local health facilities, CHWs and the school teachers. To ensure quality integrity of the study drugs under investigation and avoid harm to participant health and safety [62,63], the study team ensured that drugs procured are WHO prequalified [64] and are on the list of registered drugs by the TMDA [64]. The drugs were then procured from authorised respective manufacturing company agents in Tanzania (for DP) and in East Africa for (ASAQ). In addition, the study obtained regulatory approval from the TMDA and ethical approval from the NIMR-MRCC, Tanzania.

3.18. Statistical analysis

3.18.1. General analysis

The impact of IPTsc using DP or ASAQ *versus* controls will all be analysed using multilevel analysis, modelling Hb concentration *versus* time including hierarchical random effects to attain the primary objective. Moreover, the model will include random effects (intercept and slope) for the individual, in control of lost to follow up and any biased results. The impact of IPTsc on clinical malaria incidence will be calculated as incidence rate ratios that will be compared across the study arms/groups. Survival analysis will be used to compare malaria cases detected during intervention at month 12 and at month 20 of follow-up that includes evaluation of any rebound effect observed one year after the last malaria preventive treatment between ASAQ and DP versus the control group. To attain secondary objectives, prevalence ratios, and mean differences will be calculated. We will also assess cluster effect per school and per village or hamlet and adapt the precision of the estimates accordingly. Risk factors such as age and bed net use associated with malaria attacks will be assessed using Cox regression, all significant risks will be included in a multilevel analysis model. A per-protocol analysis including all children who have completed the three IPTsc rounds will be done. Also, intention to treat analysis will be presented. Data will be analysed using STATA or R statistical software.

3.18.2. Qualitative analyses

Transcripts and field notes will be imported into QSR NVivo 11 qualitative data analysis software for analysis using an inductive and deductive approach. Coding will occur in parallel with data collection, using a codebook based on initial research questions and with additional codes added as themes emerge from the data.

3.18.3. Cost-effectiveness analysis

The effectiveness of implementation of IPTsc is a major determinant of its health impact under operational conditions. In this aspect, cost-effectiveness analysis is an important tool to support and guide policy decision on deployment of new interventions. This will be estimated by assessing the implementation cost (FTE, transport, price scenarios, etc.), the study impact as well as possible synergies with other school health intervention programs [65]. To quantify the investment needs and financial liabilities for implementation of the IPTsc intervention, we will design an initial economic model based on preliminary cost effectiveness findings from the study. Therefore, basing on these findings, the study will come up with possible options for funding and implementation at a national or international level.

3.18.4. Safety analysis

Side-effects as well as all non-serious AEs and SAEs following the administration of any study drug will be recorded starting day 0. All events will be graded by severity and relationship to the study treatment. The number and proportion of patients experiencing any AE, any SAE, and any drug-related SAE will be compared between treatment groups and control using Fisher's exact test. The risk of experiencing an adverse event will then be estimated and compared with control using χ^2 tests. Since all children are recruited simultaneously, there will be no interim analysis.

3.19. Dissemination of results, authorship and publications

A kick-off meeting involving representatives from the Ministries of health (MoHCDGEC), education and local govenments (PO-RALG) was conducted at the beginning of the preparatory phase in September 2017 where, general strategic issues and contents of the study were specified including justification, procedures, risks and benefits of the trial. These meetings will continue on regular basis or as need arise throughout the trial to review and address trial implementation challenges and progress.

The study strategy and its possible implications will be discussed with the several cross-cutting stakeholders involved in school health at Ministerial level, NMCP, Regional and District implementers, teachers and community before the start of the trial. On completion of the study, results will be presented to the communities where the trial was undertaken, to local health authorities (at regional and district level) and to the NMCP as well as in the international and local conferences (oral and posters), peer reviewed scientific journal and press. Policy briefs will be prepared and published in public domain and media for consumption by the policy makers to support its subsequent implementation, as appropriate. Drug resistance data from the trial and related studies will be submitted to Worldwide Antimalarial Resistance Network (WWARN).

Authors will include all investigators that have participated and contributed in the trial. Authorship and publications emanating from this trial will depend on the NIMR publication policy and the principles for authorship criteria of the International Committee of Medical Journal Editors. The manufacturer of the trial medication will be provided with a draft of the manuscript but will have no role in review, data interpretation, or writing of the article.

3.20. Ethical approval and consent to participate

All research activities are conducted in accordance with the standards and codes of conduct accepted by the ICH guidelines. The study obtained ethical clearance from NIMR-MRCC with approval number NIMR/HQ/R.8a/Vol.IX/2818 and NIMR/HQ/R.8c/Vol.I/668 (for amendment) also NIMR/HQ/R.8c/Vol.I/1276 for ethical clearance extension. We obtained regulatory approval from the TMDA with approval number TFDA0017/CTR/0018/07. Prior to start of the trial, permission was obtained from the local governments (PO-RALG), the DMO/CHMT, Village administration, school committee and school parents' or guardian's meetings. No real or perceived coercion to participate was done. Written informed consent was obtained from the parents/guardians for all children before enrollment. An assent was obtained from children who were 11-years-old or older.

The consent forms were translated from English into Swahili, a language spoken by almost all study participants. Written informed consent from parents or guardians and assent were obtained from each participant, two copies were signed by respondents, one copy was given to study participant and the other retained by study team. Whenever a parent or guardian was non-literate, the consent was read to them in most cases in the presence of a literate witness. The participants and parents or guardians were asked questions on the study information (the purpose of the study, the procedures to be followed, and the risks and benefits of participation) to test for comprehension of their understanding of the study. The study team also stressed that participation is voluntary, that any participant may withdraw from the study at any time, and that neither refusal to participate nor withdrawal from the study will have any adverse consequences on future healthcare provided at the study area or elsewhere or even jeopardize their relation with school teachers. Confidentiality was also explained in details to participants and their parents or guardians.

The study team did their best to ensure participants who chose to be a part of the study feel adequately informed of its purpose, nature, procedures, risks, hazards and benefits. To achieve this, trial staff worked closely with local government officials, health officials and community members and religious leaders to incorporate a nuanced understanding of local customs, beliefs and perceptions into the informed consent process.

A copy of the information sheet and the written consent form in English and in Swahili are available for review by the Editor-in-Chief of the Journal.

3.21. Timeline

The study is planned for a period of 20 months; these includes 6 visits of 4 months intervals. In between visits there are monthly visits for supervision and collection of attendance and illness information at each school. The study field work started on March 23rd, 2019 and completed field baseline activities on May 10th, 2019. Other follow up timelines are as described in Table 1.

3.22. Protocol amendments

If protocol amendments are needed, approval is obtained from all parties including UA, NIMR, MRCC and TFDA.

4. Discussion

The importance of IPTsc has been documented in several studies [7,8,14,65]. This study aims to assess the impact of IPTsc on all clinical malaria incidences which is the most self-evident. However, there may be a risk of under or incorrect reporting of cases [66]. We therefore use the Hb change to capture the impact of intervention on symptomatic and asymptomatic infections, as well as sub-patent infections. It allows paired measurements and is less vulnerable to probable 'under-reporting'. Several other studies [8,27] have used Hb as a primary end point. However, clinical malaria incidence is our co-primary objective.

There is evidence that IPTi using SP enhanced development of naturally acquired immunity (NAI) to malaria [67] and in some cases stopping interventions led to rebound of malaria [68–71]. Therefore, in this study we will also explore the impact of IPTsc to naturally acquired immunity to malaria in school children. Studies [56,57,72–74] have shown possibility of using dry blood spot in filter papers to address malaria serology and parasite resistance [56]. Also, given the possibility of developing drug resistance or shift of sensitivity to aminoquinoline antimalarials [31,32], we will explore single nucleotide polymorphisms (SNPs) of relevance for PQ, AQ and artemisinin resistance to be more informative to policy makers [53,54]. This will contribute to inform policy makers on most forms of epidemiological impact of IPTsc.

In Tanzania, the national school health programme (NSHP), combines schistosomiasis and STH control package under integrated neglected tropical diseases (NTD) programme [75], which implements annual mass drug administration (MDA) using albendazole and mostly targets school children [75,76]. Therefore, IPTsc may be integrated in NSHP with the same platform to ensure pragmatic feasibility at low implementation cost and hence play a major role on improving cognitive ability in school aged children. This study is expected to provide systematic evidence to the operational feasibility of this approach.

There are limited antimalarial drugs with longer prophylactic effect,

therefore, we anticipate that some of our study participants may get infected at some points when the drug wanes out. We aim to assess if our four monthly approach is at least able to clear parasitaemia and reduce burden on affected children, giving time for improvement on Hb generation. The approach is expected to maintain natural immunity to malaria that is currently existing in endemic settings. Pragmatically , giving the drugs on monthly bases is operationally challenging, costly, and may aggrevate the risk of drug resistance due to high drug pressure. Also, most of school activities would be interfered in this case given it's the teachers who would be mostly involved. A study conducted in Uganda on a monthly DP delivery was associated with DP polymorphism and increased adverse events compared to a 4 monthly delivery [31].

The addition of one-year assessment of rebound effect would complement the study. In this study we provide ACTs (DP or ASAQ) three times a year. The dosing formulation (once daily for 3 days) provides an opportunity for increased compliance. i.e. administered at school under direct observation, rather than been administered at homes, where a parent/guardian may see somehow illogical to take the medication with no symptoms noted. Therefore, this study is designed to ensure that, if this approach becomes a school health policy, it will be pragmatically more likely possible to implement through an integrated school health programme [75,77] and will complement existing malaria preventive measures such as use of ITNs.

Consent for publication

Not applicable.

Availability of data and material

The datasets that are generated in the current study will be available from the corresponding author on reasonable request and approval by the collaborating institutions and signing the data transfer agreement (DTA) from NIMR [78].

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Authors' contributions

GM, VB, JPAL and JPVg conceptualised the idea. GM, VB wrote the study protocol and the trial essential documents. FF, DTRM, SG and SN contributed to the essential documents writing. GM, VB and JPAL did the approval procedures of the protocol by ethical committees and regulatory authorities. GM, VB, DTRM, GM, RM, EK and JPAL implement the study protocol in the field. JL and JPVg reviewed the protocol and will supervise the conduct of the trial. JPVg carries the sponsorship of the study. All authors read and approved the submitted manuscript.

Authors' information

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Trial status

On follow up.

Protocol version

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Declaration of competing interest

The authors declare that they have no competing interests.

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