Weekly dihydroartemisinin–piperaquine versus monthly sulfadoxine–pyrimethamine for malaria chemoprevention in children with sickle cell anaemia in Uganda and Malawi (CHEMCHA): a randomised, double-blind, placebo-controlled trial

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Summary

Background In many sub-Saharan African countries, it is recommended that children with sickle cell anaemia receive malaria chemoprevention with monthly sulfadoxine–pyrimethamine or daily proguanil as the standard of care. However, the efficacy of these interventions is compromised by high-grade antifolate resistance of *Plasmodium falciparum* and poor adherence. We aimed to compare the efficacy of weekly dihydroartemisinin–piperaquine and monthly sulfadoxine–pyrimethamine for the prevention of clinical malaria in children with sickle cell anaemia in areas with high-grade sulfadoxine–pyrimethamine resistance of *P falciparum* in Uganda and Malawi.

Methods We did an individually randomised, parallel group, double-blind, placebo-controlled trial at two hospitals in Uganda and two hospitals in Malawi. Children (aged 6 months to 15 years) with sickle cell anaemia with a bodyweight of at least 5kg were randomly assigned (1:1) by computer-generated block randomisation, stratified by site and weight category, to receive either weekly dihydroartemisinin–piperaquine (approximately 2·5 mg per kg bodyweight dihydroartemisinin and 20 mg per kg bodyweight per day piperaquine) or monthly sulfadoxine–pyrimethamine (approximately 25 mg per kg bodyweight sulfadoxine and 1·25 mg per kg bodyweight). Placebos matching the alternative treatment were used in each treatment group to maintain masking of the different dosing schedules from the participants and caregivers, study staff, investigators, and data analysts. All children younger than 5 years received penicillin twice daily as standard of care. The primary endpoint was the incidence of clinical malaria, defined as a history of fever in the preceding 48 h or documented axillary temperature of 37·5°C or higher plus the detection of *P falciparum* parasites on microscopy (any parasite density). Secondary efficacy outcomes were any malaria parasitaemia (on either microscopy or malaria rapid diagnostic test), all-cause unscheduled clinic visits, all-cause and malaria-specific hospitalisation, sickle cell anaemia-related events (including vaso-occlusive crises, acute chest syndrome, stroke), need for blood transfusion, and death. All primary and secondary outcomes were assessed in the modified intention-to-treat population, which included all participants who were randomly assigned for whom endpoint data were available. Safety was assessed in in all children who received at least one dose of the study drug. Complete case analysis was conducted using negative-binomial regression. This study was registered with Clinicaltrials.gov, NCT04844099.

Findings Between April 17, 2021, and May 30, 2022, 725 participants were randomly assigned; of whom 724 were included in the primary analysis (367 participants in the dihydroartemisinin–piperaquine group and 357 participants in the sulfadoxine–pyrimethamine group). The median follow-up time was 14·7 months (IQR 11·2–18·2). The incidence of clinical malaria was 8·8 cases per 100 person-years in the dihydroartemisinin–piperaquine group and 43.7 events per 100 person-years in the sulfadoxine–pyrimethamine group (incidence rate ratio [IRR] 0·20 [95% CI 0·14–0·30], p<0·0001). The incidence of hospitalisation with any malaria was lower in the dihydroartemisinin–piperaquine group than the sulfadoxine–pyrimethamine group (10·4 *vs* 37·0 events per 100 person-years; IRR 0·29 [0·20–0·42], p<0·0001) and the number of blood transfusions was also lower in the dihydroartemisinin–piperaquine group than the sulfadoxine–pyrimethamine group (52·1 *vs* 72·5 events per 100 person-years; IRR 0·70 [0·54–0·90], p=0·006). The incidence of all-cause unscheduled clinic visits and all-cause hospitalisations were similar between the two groups, however, participants in the dihydroartemisinin–piperaquine group had more clinic visits unrelated to malaria (IRR 1·12 [1·00–1·24], p=0·042) and more hospitalisations with lower respiratory tract events (16·5 *vs* 8·5 events per 100 person-years; IRR 1·99 [1·25–3·16], p=0·0036) than participants in the sulfadoxine–pyrimethamine group. The number of serious adverse events in the dihydroartemisinin–piperaquine group was similar to that in the sulfadoxine–pyrimethamine group (vaso-occlusive crisis [154 of 367 participants dihydroartemisinin–piperaquine group *vs* 132 of 357 participants in the sulfadoxine–pyrimethamine group] and suspected sepsis [115 participants *vs* 92 participants]),

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For the Chichewa translation of the abstract see Online for appendix 1

For the Acholi translation of the abstract see Online for appendix 2

For the Lusoga translation of the abstract see Online for appendix 3

For the Luganda translation of the abstract see Online for appendix 4

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with the exception of acute chest syndrome or pneumonia (51 participants *vs* 32 participants). The number of deaths were similar between groups (six [2%] of 367 participants in the dihydroartemisinin–piperaquine group and eight (2%) of 357 participants in the sulfadoxine–pyrimethamine group).

Interpretation **Malaria chemoprophylaxis with weekly dihydroartemisinin–piperaquine in children with sickle cell anaemia is safe and considerably more efficacious than monthly sulfadoxine–pyrimethamine. However, monthly sulfadoxine–pyrimethamine was associated with fewer episodes of non-malaria-related illnesses, especially in children 5 years or older not receiving penicillin prophylaxis, which might reflect its antimicrobial effects. In areas with high *P falciparum* antifolate resistance, dihydroartemisinin–piperaquine should be considered as an alternative to sulfadoxine–pyrimethamine for malaria chemoprevention in children younger than 5 years with sickle cell anaemia receiving penicillin-V prophylaxis. However, there is need for further studies in children older than 5 years.**

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Introduction

Sickle cell anaemia is one of the most common inherited single-gene disorders worldwide.[1] Children with sickle cell anaemia often have repeated ill health and crises (painful episodes, haemolysis, and severe anaemia), chronic morbidity, and premature deaths. Many of these crises are precipitated by febrile illnesses, including malaria.

Children with the heterozygosity for the sickle cell trait (HbAS) are strongly protected against malaria,[2] which is thought to be the main reason why the genetic mutation in the β globin gene (*HBB*) that codes for sickle haemoglobin (HbS) has been retained in African populations. Individuals with homozygous sickle cell anaemia also have a lower risk of malaria compared with

Research in context

Evidence before this study

We searched PubMed from database inception to July 31, 2024, for published articles using the search terms "sickle cell disease", "sickle cell anaemia", "trial", "effectiveness", "efficacy", "malaria chemoprophylaxis", and "malaria chemotherapy", with no language restrictions. Additionally, we searched for bibliographies of all the studies that were included. Our search identified eight eligible studies (four from Nigeria, one each from Senegal and Kenya, and two from Uganda) involving 1266 participants. The interventions included weekly chloroquine, daily proguanil, monthly pyrimethamine, sulfadoxine–pyrimethamine or sulfadoxine–pyrimethamine-amodiaquine, monthly or mefloquine-artesunate, and monthly dihydroartemisinin–piperaquine. These interventions were compared against either a placebo, or daily proguanil, weekly chloroquine, or monthly sulfadoxine–pyrimethamine. Overall, participants who received malaria prophylaxis were less likely to have detectable malaria parasitaemia or present with episodes of clinical malaria compared with placebo. Chemoprophylaxis reduced the number of episodes of sickle cell anaemia complications and increased mean haemoglobin values. However, the efficacy of proguanil and sulfadoxine–pyrimethamine based interventions might be hindered by high-level antifolate resistance of *Plasmodium falciparum* to sulfadoxine–pyrimethamine and proguanil and low adherence to daily proguanil. Monthly dihydroartemisinin–piperaquine has shown great promise for malaria chemoprevention in infants, children, and pregnant women. Modelling studies suggest that weekly dihydroartemisinin–piperaquine achieves higher steady-state piperaquine trough concentrations with lower peak concentrations and less dose-dependent QT prolongation than monthly dosing and is predicted to be more effective and exerts less selection pressure for piperaquine resistance. It is also suggested that weekly administration is less affected by missing occasional doses than monthly administration.

Added value of this study

This is the first trial to evaluate the efficacy of weekly dihydroartemisinin–piperaquine for malaria chemoprophylaxis in children with sickle cell anaemia. The trial showed that in areas of Africa with high levels of antifolate resistance among malarial parasites, weekly dihydroartemisinin–piperaquine is more efficacious in preventing malaria than monthly sulfadoxine–pyrimethamine in children. However, among children aged 5 years or older who were not on penicillin prophylaxis, the incidence of lower respiratory tract events such as pneumonia or acute chest syndrome was higher than children aged younger than 5 years on penicillin prophylaxis, which is likely to reflect the antimicrobial effects of sulfadoxine–pyrimethamine.

Implications of all the available evidence

Ministries of Health in regions with high antifolate resistance of *P falciparum* in sub-Saharan Africa could consider replacing monthly sulfadoxine–pyrimethamine in children younger than 5 years with sickle cell anaemia receiving penicipllin prophylaxis. However, there is need for further studies in children older than 5 years.

those without, but morbidity and mortality is higher among these individuals when admitted to hospital with malaria.[3] The increased risk might partly be related to worsened anaemia, sickle cell crises, and bacteraemia that can occur with malaria.

At present, malaria chemoprevention with monthly sulfadoxine–pyrimethamine or daily proguanil is the standard of care in patients with sickle cell anaemia in several African countries, including Uganda and Malawi. However, high-level resistance of *Plasmodium falciparum* to sulfadoxine–pyrimethamine in eastern and southern Africa[4] threatens the antimalarial efficacy of both sulfadoxine–pyrimethamine and proguanil because they are antifolate drugs with similar modes of action. Furthermore, the uptake of daily proguanil is low due to poor adherence to daily dosing,[5–7] frequent stock shortages, and cost barriers.[8]

A growing number of studies support the use of dihydroartemisinin–piperaquine for malaria chemoprevention in infants, children, and pregnant women[9,10] and in sickle cell anaemia.[11] In this study, we aimed to compare the efficacy and safety of weekly dihydroartemisinin–piperaquine compared with monthly sulfadoxine–pyrimethamine for the prevention of malaria in children with sickle cell anaemia living in areas with moderate to intense malaria transmission and where *P falciparum* has high levels of resistance to sulfadoxine–pyrimethamine.

Methods

Study design and participants

This was an individually randomised, parallel-group, double-blind, placebo-controlled trial done at two hospitals in Uganda (Jinja Regional Referral Hospital [Jinja] and Kitgum General Hospital [Kitgum]) and two hospitals in Malawi (Queen Elizabeth Central Hospital [Blantyre] and Kamuzu Central Hospital [Lilongwe]) in areas with high levels of *P falciparum* resistance to sulfadoxine–pyrimethamine.[12,13]

The trial protocol has been published previously.[14] Briefly, eligible children were aged 6 months to 15 years, had sickle cell anaemia (all had HbSS) detected by haemoglobin electrophoresis or isoelectric focusing, with a bodyweight of 5 kg or higher. Children with other known chronic diseases, those who were receiving daily cotrimoxazole prophylaxis, or were participating in another trial were excluded.

Written consent was obtained from the parent or caregiver (and assent from children aged ≥8 years) for all participants. The study was approved by Makerere University School of Medicine Research and Ethics Committee (2020-103), Liverpool School of Tropical Medicine Research Ethics Committee (19.105), the Regional Committee for Medical and Health Research Ethics, western Norway (30992) and the National Health Sciences Research Committee in Malawi (19/11/2442). The trial is registered at ClinicalTrials.gov, NCT04844099.

Randomisation and masking

Participants were randomly assigned (1:1) to receive weekly dihydroartemisinin–piperaquine plus monthly sulfadoxine–pyrimethamine placebo or monthly sulfadoxine–pyrimethamine plus weekly dihydroartemisinin–piperaquine placebo. Randomisation was done by an independent statistician using computer-generated permuted block randomisation with varying block sizes (4, 6, or 8), stratified by site and weight (5 to <8, 8 to <11, 11 to <17, 17 to <25, 25 to <36, and 36 to <60 kg). The randomisation list and allocation sequence were sent to the trial pharmacists in Uganda and Malawi to prepare sequentially numbered, sealed opaque envelopes for each participant with the randomisation assignment. The pharmacists prepared the subject-specific study drugs by site and weight bands. At each study site, the opaque envelopes were opened sequentially on participant enrolment by the responsible study staff. Eligible participants were allocated in the order of their study identification number by drawing the next sequentially numbered sealed envelope. The use of matching placebos enabled the different dosing schedules to be concealed from participants and caregivers, study staff, investigators, and data analysts.

Procedures

At enrolment, sociodemographic information and medical history were recorded and a physical exam was performed. 2–4 mL of venous blood was drawn for complete blood count, malaria microscopy, malaria rapid diagnostic test, and later measurement of piperaquine drug levels (appendix 5 p 2). Participants assigned to the weekly dihydroartemisinin–piperaquine group were administered a fixed dose of scored dispersible tablets containing 20 mg dihydroartemisinin and 160 mg piperaquine (Fosun Pharma, Shanghai, China) and monthly placebo (Fosun Pharma). Tablets were administered orally once a week at a dose of approximately 2·5 mg per kg bodyweight per day dihydroartemisinin and 20 mg per kg bodyweight per day piperaquine, based on participants' weight category (appendix 5 p 2). Participants assigned to the monthly sulfadoxine–pyrimethamine group were administered tablets containing 500 mg sulfadoxine and 25 mg pyrimethamine (Fosun Pharma) and weekly placebo (Fosun Pharma). Tablets were administered orally once a month at approximate doses of 25 mg per kg bodyweight sulfadoxine and 1·25 mg per kg bodyweight pyrimethamine. Dihydroartemisinin–piperaquine and dihydroartemisinin–piperaquine placebo were supplied as blister packs, which were unidentifiable from each other, containing three tablets each. The sulfadoxine–pyrimethamine and sulfadoxine–pyrimethamine placebo were also supplied in similar blister packs containing three tablets each. Depending on the participant's weight category, each weekly and monthly dose for the next 2 months was dispensed in transparent, clearly labelled

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zip-locked plastic bags. The interventions were given until study end.

The first dose of each intervention was given with water in the clinic under direct observation. Subsequent doses were given to the caregiver to administer at home. Parents or caregivers were advised to administer the drugs at around the same time each day, and if the participant vomited within 30 min, to repeat the full dose once.

Parents or caregivers were educated on the care of children with sickle cell anaemia, including hydration, care of the child, pain management, and when to seek medical help. All parents or caregivers received long-lasting insecticide-treated mosquito nets, paracetamol, folic acid (0·4 mg per day), penicillin if the child was younger than 5 years, and the child's vaccinations were updated if behind the national vaccination schedule. Participants attended scheduled clinics with their caregivers every 2 months to receive their next doses of study medication and unscheduled visits if they were unwell. The study provided standard-of-care clinical services for all unscheduled visit to the study clinic by a participant due to ill health or an acute complication of sickle cell anemia (referred to hereafter as unscheduled clinic visit). A history of recent illness and medication use was obtained at each visit, a clinical examination was performed, and a blood sample was taken for malaria diagnosis. If the participant did not attend the scheduled follow-up visits, they were contacted by phone to remind them and visited at home if so required. At each scheduled visit, blood sampling was done similarly to that on enrolment. Medication adherence was assessed through pill counts at each scheduled and unscheduled visit. Participants with less than 80% adherence had additional adherence counselling.

Participants were admitted to hospital if they developed severe complications of sickle cell anaemia. In addition to a blood slide for malaria microscopy, participants with an axillary temperature higher than 38·0°C had blood and urine (if the urine dipstick examination was abnormal) bacterial cultures taken, were admitted to hospital, and given intravenous ceftriaxone. For children younger than 5 years, urine was collected in paediatric sterile urine cups and for those aged 5 years and older, universal wide-mouth sterile urine cups were used. The samples were inoculated on cysteine-lactose-electrolyte deficient agar using calibrated loops.

Blood cultures were aseptically collected in bottles (BACTEC; Becton Dickinson, Franklin Lakes, NJ, USA) and incubated in a BACTEC FX Blood Culture System (Becton Dickinson). Positive cultures were Gram stained and subcultured. Standard tests were used for the identification of Gram-negative and Gram-positive organisms and antimicrobial susceptibility tests were done. Further management was guided by the malaria blood slide and culture results and clinical improvement. All other sickle cell anaemia-related and non-sickle cell anaemia-related events, such as vaso-occlusive crises, were documented and reported. Lower respiratory tract infections and acute chest syndrome are difficult to distinguish clinically, therefore, the two were combined and defined as lower respiratory tract events.

Children with severe malaria received at least three doses of parenteral artesunate followed by a 3-day course of artemether–lumefantrine. Participants with severe anaemia (haemoglobin concentration <5·0 g/dL) received a blood transfusion. Participants with uncomplicated malaria were treated with artemether–lumefantrine, and the next weekly dose of dihydroartemisinin–piperaquine or dihydroartemisinin–piperaquine placebo or the monthly dose of sulfadoxine–pyrimethamine or sulfadoxine–pyrimethamine placebo was delayed until the 3-day course of artemether-lumefantrine was completed.

Adverse events and serious adverse events were assessed at each scheduled and unscheduled visit and graded using standardised severity criteria according to the Common Terminology Criteria for Adverse Events. Events were coded using Medical Dictionary for Regulatory Activities coding. The diagnoses during unscheduled visits were coded using the International Classification of Disease, 10th edition, for children.

We performed an intensive pharmacokinetic and pharmacodynamic study in 30 participants at 0, 1, 2, 3, 4, 6, and 8 h and on days 3 and 7 after the first dose to determine the time after administration of a dose of dihydroartemisinin–piperaquine at which QT prolongation (if present) was expected to be greatest (T_{max}); the maximum corrected QT interval prolongation on electrocardiograms [(ECGs), if any, and the association between QTc prolongation and serum piperaquine levels. The QTc interval was calculated using Fredericia's correction formula. Additionally, we conducted a sparse pharmacokinetic and pharmacodynamic study, in which a small number of samples are drawn per participant, in a subset of 192 participants, which involved weekly ECGs and pharmacokinetic sampling at T_{max} for the first 6 weeks and then at 3, 4, and 12 months. The rationale for this approach was to precisely identify T_{max} to inform optimal timing for subsequent ECG monitoring, evaluate acute QT effects after individual doses, assess potential cumulative effects over 6 weeks of weekly dosing, and examine long-term safety with extended use over 12 months. Piperaquine concentrations were measured using a validated liquid chromatography with tandem mass spectrometry method with a lower limit of quantification of 1·2 ng/mL at the Mahidol-Oxford Tropical Research Unit in Bangkok, Thailand.[15]

Outcomes

The primary efficacy outcome measure was the incidence of clinical malaria, defined as a history of fever in the preceding 48 h or documented axillary temperature of 37·5°C or higher plus the detection of *P falciparum* parasites on microscopy (any parasite density) at

scheduled and unscheduled visits (appendix 5 p 2). Malaria diagnosis was performed by WHO-certified microscopists at each site. Two independent on-site microscopists examined each thick and thin blood smear. Discordant readings were resolved by a third centrally-located expert microscopist. Secondary efficacy outcomes were any malaria parasitaemia (on either microscopy or malaria rapid diagnostic test), all-cause unscheduled clinic visits, all-cause and malaria-specific hospitalisation, sickle cell anaemia-related events (including vaso-occlusive crises, acute chest syndrome, stroke), need for blood transfusion, and death. Additional secondary outcomes were acceptability, user preferences, uptake, and potential for future roll-out of weekly dihydroartemisinin–piperaquine, safety of cumulative dosing of dihydroartemisinin–piperaquine, quality of life, cost effectiveness, and development of genetic markers of resistance to dihydroartemisinin–piperaquine. All pre-specified additional secondary outcomes will be published separately.

Statistical analysis

The study was designed to detect at least a 50% reduction in the incidence of clinical malaria from 0·2 cases per person-year in the sulfadoxine–pyrimethamine group to 0·1 cases per person-year in the dihydroartemisinin–piperaquine group[16] with 90% power and a two-sided α of 0·05 and required 824 person-years of observation overall (412 in each group; eg, 548 participants followed up for an average of 18 months, or 824 participants followed-up for 12 months), allowing for 20% loss to follow-up. Negative binomial regression with a log-link function and log follow-up time as an offset was used for the primary endpoint and other count variables to obtain incidence rate ratios (IRRs), incidence rate differences, and 95% CIs. The number-needed-to-treat (NNT) to avert one episode of clinical malaria was calculated as the inverse of the incidence rate difference per the mean duration of follow-up. The NNT represents the average number of patients who need to be treated with the intervention (weekly dihydroartemisinin–piperaquine) compared with the control (monthly sulfadoxine–pyrimethamine) to prevent one additional case of clinical malaria over the study period. A lower NNT indicates a more effective intervention. The unadjusted (crude) analysis was the primary analysis and included the stratification factors study site and weight band in all models. Secondary, covariate-adjusted analyses were done using prespecified baseline covariates in addition to site and weight band.

The primary and secondary efficacy outcomes were assessed in the modified intention-to-treat (ITT) population, which included all participants who were randomly assigned for whom endpoint data were available. To examine the effects of taking hydroxyurea in addition to the study drugs, in a post-hoc analysis, we fitted a negative-binomial model of the number of clinical malaria episodes (outcome) with the study group (sulfadoxine–pyrimethamine *vs* dihydroartemisinin–piperaquine) as the main predictor adjusting for study site, weight band, and hydroxyurea (first as duration on hydroxyurea and second as having taken hydroxyurea during the study or not). Safety was assessed in all children who received at least one dose of the study drug. All analyses were prespecified (unless otherwise indicated as post-hoc). The number of children who had adverse events, the type of event, total number of events, and the incidence per 100 person-years are presented per treatment group. p values of less than 0·05 were considered to indicate statistical significance. All analyses were done using Stata (version 18.0).

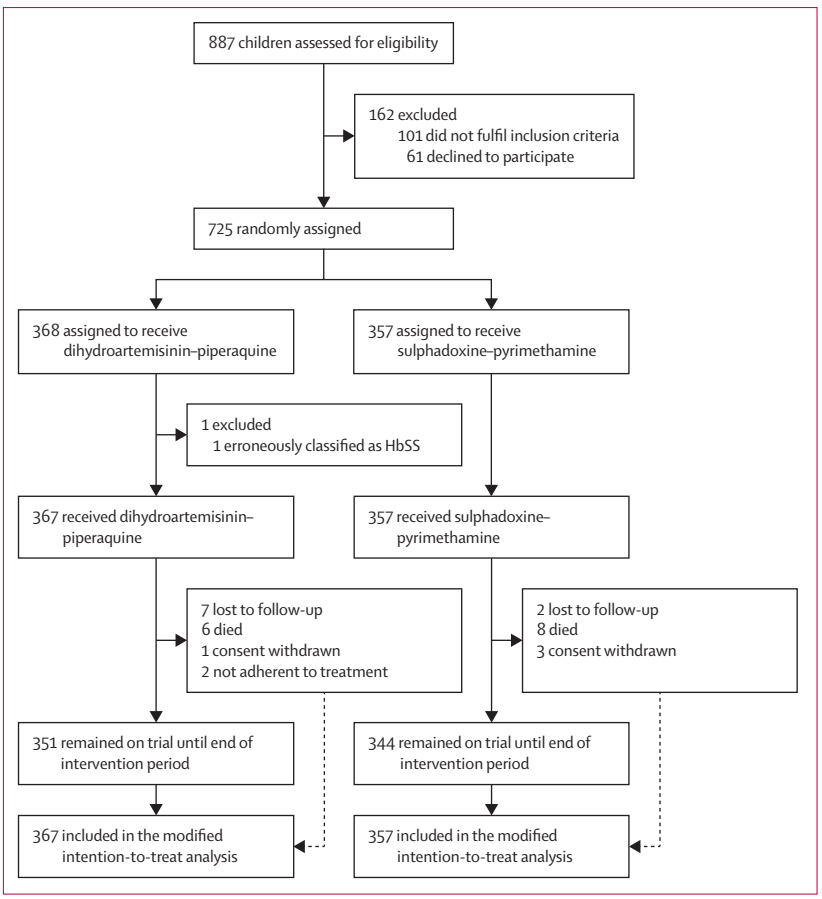

Figure 1: **Trial profile**
HbSS=homozygous sickle cell anaemia.

Role of the funding source

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

Results

Between April 17, 2021, and May 30, 2022, 887 children with sickle cell anaemia were screened for eligibility, of whom 725 were randomly assigned (368 to the

	Dihydroartemisinin–piperaquine (n=367)	Sulfadoxine–pyrimethamine (n=357)
Age, years	6·8 (4·2–10·7)	7·2 (4·4–10·7)
Sex		
Male	193 (53%)	176 (49%)
Female	174 (47%)	181 (51%)
Study site, n (%)		
Jinja Regional Referral Hospital	144 (39%)	137 (38%)
Kitgum General Hospital	95 (26%)	95 (27%)
Queen Elizabeth Central Hospital	32 (9%)	30 (8%)
Kamuzu Central Hospital	96 (26%)	95 (27%)
Bodyweight, kg	19·2 (14·8–25·3)	19·7 (15·0–26·0)
Weight-for-age Z score		
Normal (less than –2)	267 (73%)	262 (73%)
Underweight (–3 to–2)	68 (19%)	68 (19%)
Severe wasting (less than –3)	32 (9%)	27 (8%)
Height-for-age Z score		
Normal (less than –2)	233 (64%)	244 (69%)
Stunted (–3 to–2)	89 (24%)	63 (18%)
Severe stunting (less than –3)	44 (12%)	47 (13%)
Current school grade of the participant		
Not in school	83 (23%)	90 (25%)
Pre-school	107 (29%)	90 (25%)
Primary school	170 (46%)	174 (49%)
Secondary school	7 (2%)	3 (1%)
Level of education of primary caregiver		
No formal education	14 (4%)	14 (4%)
Primary school education	163 (47%)	151 (43%)
Secondary school education	135 (39%)	145 (42%)
Tertiary or university education	37 (11%)	38 (11%)
Has ever had a blood transfusion	291 (79%)	279 (78%)
Was taking hydroxyurea on enrolment	135 (37%)	122 (34%)
Admitted to hospital in the previous year	224 (67%)	216 (67%)

Data are median (IQR) or n (%).

Table 1: **Baseline demographic and clinical characteristics (modified intention-to-treat population; n=724)**

dihydroartemisinin–piperaquine group and 357 to the sulfadoxine–pyrimethamine group). After randomisation, one child with HbAS, who was erroneously classified as HbSS, was withdrawn. The remaining 724 participants were included in the analysis (367 participants in the dihydroartemisinin–piperaquine group and 357 participants in the sulfadoxine–pyrimethamine group; figure 1). 471 participants were from Uganda and 253 from Malawi; 369 (51%) were male and 335 (49%) were female. The median age at enrolment was 7 years (IQR 4·3–10·7). Participants were followed up for a median of 14·7 months (IQR 11·2–18·2). Recruitment was stopped when at least 353 participants per group were recruited, assuming that the median follow-up time would be around 14 months per person. The study was concluded on July 10, 2023, once the predetermined cumulative person-years of follow-up were reached. The median number of hospital admissions in the previous year was 1·0 (IQR 0·0–3·0) and 570 (79%) of 724 participants had previously had a blood transfusion. In Malawi, 193 (76%) of 253 participants were receiving daily hydroxyurea at enrolment, compared with 64 (14%) of 471 participants in Uganda. 173 participants were later initiated on hydroxyurea between Aug 1, 2021 and Oct 31, 2022, following a revision of the treatment guidelines in Uganda. Baseline characteristics, including the number of participants receiving hydroxyurea at enrolment, were similar between the two groups (table 1).

The incidence of clinical malaria in the dihydroartemisinin–piperaquine group was 8·8 cases 100 person-years compared with 43·7 cases per 100 person-years in the sulfadoxine–pyrimethamine group (IRR 0·20 [95% CI 0·14–0·30], p<0·0001; figure 2, table 2). The number-needed-to-treat to avert one episode of clinical malaria was three. The incidence of any malaria infection (ie, *P falciparum* detected by microscopy or malaria rapid diagnostic test) was lower in the dihydroartemisinin–piperaquine group than in the sulfadoxine–pyrimethamine group (IRR 0·27 [0·20–0·37], p<0·0001) and the number of hospital admissions for malaria (ie, any hospitalisation with malaria detected by microscopy or malaria rapid diagnostic test; IRR 0·29 [0·20–0·42], p<0·0001) was also lower. Additionally, fewer blood transfusions were reported in the dihydroartemisinin–piperaquine group than in the sulfadoxine–pyrimethamine group (52·1 *vs* 72·5 events per 100 person-years; IRR 0·70 [0·54–0·90], p=0·006; table 2, table 3).

The incidence of non-malaria unscheduled clinic visits was higher in the dihydroartemisinin–piperaquine group than the sulfadoxine–pyrimethamine group (294·6 *vs* 268·3 events per 100 person-years; IRR 1·12 [95% CI 1·00–1·24], p=0·042), including for lower respiratory tract events (16·5 *vs* 8·3 events per 100 person-years; IRR 1·99 [1·25–3·16], p=0·006; table 2). In a post-hoc analysis, the incidence of hospitalisation for lower respiratory tract events in children aged 5 years and older was higher in the dihydroartemisinin–piperaquine group than the sulfadoxine–pyrimethamine group (14·7 *vs* 5·2 events per 100 person-years; IRR 2·82 [1·42–5·60], p=0·0031). No differences were observed between treatment groups among children aged younger than 5 years (20·8 events per 100 person-years in the dihydroartemisinin–piperaquine group *vs* 15·9 events per 100 person-years in the sulfadoxine–pyrimethamine group; IRR 1·27 [0·69–2·34], p=0·44; table 3).

	Dihydroartemisinin–piperaquine (n=367)		Sulfadoxine–pyrimethamine (n=357)		Unadjusted		Adjusted	
	Events, n	Events per person-years (incidence per 100-person years)	Events, n	Events per person-years (incidence per 100-person years)	IRR (95% CI)	p value	IRR (95% CI)	p value
Primary outcome								
Clinical malaria	25	39/441·6 (8·8)	103	191/437·5 (43·7)	0·20 (0·13–0·31)	<0·0001	0·20 (0·14–0·30)	<0·0001
Secondary outcomes								
All–cause sick visits	286	1340/441·6 (303·4)	254	1365/437·5 (312·0)	0·98 (0·84–1·14)	0·7794	1·00 (0·90–1·11)	0·9903
All–cause hospitalisations	227	626/441·6 (141·7)	216	698/437·5 (159·5)	0·88 (0·74–1·05)	0·1558	0·92 (0·79–1·07)	0·2718
Malaria infection	44	82/441·6 (18·6)	122	298/437·5 (68·1)	0·27 (0·19–0·38)	<0·0001	0·27 (0·20–0·37)	<0·0001
Malaria hospitalisations	30	46/441·6 (10·4)	97	162/437·5 (37·0)	0·28 (0·19–0·41)	<0·0001	0·29 (0·20–0·42)	<0·0001
Non–malaria sick visits	285	1301/441·6 (294·6)	250	1174/437·5 (268·3)	1·10 (0·95–1·28)	0·1920	1·12 (1·00–1·24)	0·0419
Non–Malaria hospitalisations	221	580/441·6 (131·3)	209	536/437·5 (122·5)	1·06 (0·89–1·27)	0·5028	1·09 (0·93–1·27)	0·3007
Vaso–occlusive crisis	154	292/441·6 (66·1)	148	298/437·5 (68·1)	0·96 (0·76–1·20)	0·6952	0·99 (0·80–1·23)	0·9291
Upper respiratory infection	18	20/441·6 (4·5)	18	20/437·5 (4·6)	1·00 (0·52–1·96)	0·9888	1·02 (0·52–1·99)	0·9566
Acute chest syndrome or pneumonia	51	73/441·6 (16·5)	32	37/437·5 (8·5)	1·93 (1·21–3·08)	0·0058	1·99 (1·25–3·16)	0·0036
Suspected sepsis	115	184/441·6 (41·7)	92	144/437·5 (32·9)	1·25 (0·95–1·65)	0·1104	1·28 (0·99–1·64)	0·0611
Death*	6	6/367 (1·6%)	8	8/357 (2·2%)	0·74 (0·25–2·15)	0·5778	..	..

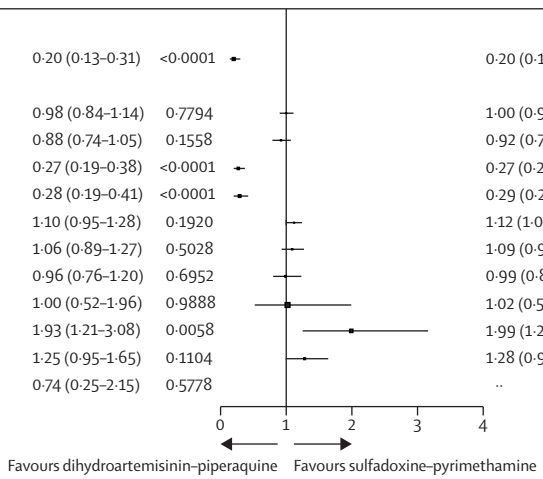

Figure 2: **Effect of chemoprevention on efficacy outcomes (modified intention-to-treat population)**
Unadjusted incidence rate values are presented for each study group. Adjusted IRRs were obtained by fitting a negative-binomial model with a log time offset adjusting for the stratification factors site and weight bands as covariates. IRR compares dihydroartemisinin–piperaquine with sulfadoxine–pyrimethamine (reference). IRR=incidence rate ratio. *For deaths, the proportion of children who died as a percentage is shown; a logistic regression model was fitted with only the study group as a covariate and a log-time offset, therefore, the relative risk is reported for this outcome .

	Dihydroartemisinin–piperaquine (n=367)			Sulfadoxine–pyrimethamine (n=357)			IRR (95% CI)*	p value
	Children with event, n	Events per person-years	Incidence (per 100 person-years)	Children with event, n	Events per person-years	Incidence (per 100 person-years)		
Primary outcome								
Clinical malaria†	25	39/441·6	8·8	103	191/437·5	43·7	0·20 (0·14–0·30)	<0·0001
Secondary outcomes								
Unscheduled all-cause clinic visits	286	1340	303·4	254	1365/437·5	312·0	1·00 (0·90–1·11)	0·99
All-cause hospitalisations	227	626/441·6	141·7	216	698/437·5	159·5	0·92 (0·79–1·07)	0·27
Any malaria parasitaemia (on either microscopy or mRDT)	44	82/441·6	18·6	122	298/437·5	68·1	0·27 (0·20–0·37)	<0·0001
Any malaria hospitalisation (malaria diagnosis on either microscopy or mRDT)	30	46/441·6	10·4	97	162/437·5	37·0	0·29 (0·20–0·42)	<0·0001
Unscheduled non-malaria clinic visits	285	1301/441·6	294·6	250	1174/437·5	268·3	1·12 (1·00–1·24)	0·042
Non-malaria hospitalisations	221	580/441·6	131·3	209	536/437·5	122·5	1·09 (0·93–1·27)	0·30
Vaso-occlusive crisis	154	292/441·6	66·1	148	298/437·5	68·1	0·99 (0·80–1·23)	0·93
Suspected sepsis	115	184/441·6	41·7	92	144/437·5	32·9	1·28 (0·99–1·64)	0·061
Upper respiratory infection	18	20/441·6	4·5	18	20/437·5	4·6	1·02 (0·52–1·99)	0·96
Acute chest syndrome or pneumonia	51	73/441·6	16·5	32	37/437·5	8·5	1·99 (1·25–3·16)	0·0036
Received blood transfusion during the study period	106	230/441·6	52·1	137	317/437·5	72·5	0·70 (0·54–0·90	0·0063
Death	6	6/367	1·6	8	8/357	2·2	0·74 (0·25–2·15)‡	0·58

IRR=incidence rate ratio. mRDT=malaria rapid diagnostic test. *Negative-binomial models were fitted with a log time offset, and adjusted for the stratification factors site and weight band; dihydroartemisinin–piperaquine versus sulfadoxine–pyrimethamine (reference). †Clinical malaria was defined as a history of fever in the preceding 48 h or documented axillary temperature higher than 37·5°C and *Plasmodium falciparum* parasites on microscopic examination of a blood smear. ‡A logistic regression model was used with treatment group as the sole predictor and a log follow-up as an offset; considering the rarity of the event (death) and the use of a time offset, the resulting estimate is reported as a relative risk rather than IRR.

Table 2: **Primary and secondary outcomes**

In a post-hoc analysis, we examined the potential confounding effects of hydroxyurea therapy on the effects of dihydroartemisinin–piperaquine. At enrolment, 135 (37%) of 367 participants in the dihydroartemisinin–piperaquine group and 122 (34%) of 357 participants in the sulfadoxine–pyrimethamine were receiving hydroxyurea. An additional 173 participants (78 participants in the dihydroartemisinin–piperaquine

	Children younger than 5 years (n=221)				Children 5 years or older (n=503)			
	Events/person-years (unadjusted incidence per 100 person-years)		IRR (95% CI)*	p value	Events/person-years (unadjusted incidence per 100 person-years)		IRR (95% CI)*	p value
	Dihydroartemisinin–piperaquine (n=113)	Sulfadoxine–pyrimethamine (n=108)			Dihydroartemisinin–piperaquine (n=254)	Sulfadoxine–pyrimethamine (n=249)		
Primary outcome								
Clinical malaria	12/134·9 (8·9)	65/132·0 (49·2)	0·18 (0·09–0·35)	<0·0001	27/306·7 (8·8)	126/305·5 (41·2)	0·23 (0·14–0·37)	<0·0001
Secondary outcomes								
Unscheduled all-cause clinic visits	497/134·9 (368·3)	524/132·0 (397·0)	0·93 (0·80–1·08)	0·32	843/306·7 (274·9)	841/305·5 (275·3)	1·06 (0·92–1·22)	0·44
All-cause hospitalisations	230/134·9 (170·4)	259/132·0 (196·2)	0·87 (0·68–1·11)	0·27	396/306·7 (129·1)	439/305·5 (143·7)	0·95 (0·78–1·16)	0·64
Any malaria parasitaemia (malaria diagnosis on either microscopy or mRDT)	21/134·9 (15·6)	98/132·0 (74·2)	0·19 (0·11–0·34)	<0·0001	60/306·7 (19·6)	200/305·5 (65·5)	0·32 (0·22–0·46)	<0·0001
Any malaria hospitalisation (malaria diagnosis on either microscopy or mRDT)	16/134·9 (11·8)	50/132·0 (37·9)	0·30 (0·16–0·58)	0·0003	30/306·7 (9·8)	112/305·5 (36·7)	0·28 (0·17–0·45)	<0·0001
Unscheduled non-malaria clinic visits	485/134·9 (359·4)	459/132·0 (347·7)	1·03 (0·88–1·21)	0·72	816/306·7 (266·0)	715/305·5 (234·0)	1·18 (1·02–1·36)	0·021
Non-malaria hospitalisations	214/134·9 (158·6)	209/132·0 (158·3)	1·00 (0·78–1·29)	0·99	366/306·7 (119·3)	327/305·5 (107·0)	1·15 (0·94–1·41)	0·17
Vaso-occlusive crisis	93/134·9 (68·9)	97/132·0 (73·5)	0·93 (0·66–1·32)	0·70	199/306·7 (64·9)	201/305·5 (65·8)	1·05 (0·80–1·39)	0·74
Suspected sepsis	83/134·9 (61·5)	65/132·0 (49·2)	1·32 (0·88–1·97)	0·18	101/306·7 (32·9)	79/305·5 (25·9)	1·26 (0·91–1·75)	0·16
Upper respiratory infection	5/134·9 (3·7)	7/132·0 (5·3)	0·70 (0·21–2·36)	0·56	15/306·7 (4·9)	13/305·5 (4·3)	1·17 (0·53–2·62)	0·69
Lower respiratory tract events	28/134·9 (20·8)	21/132·0 (15·9)	1·27 (0·69–2·34)	0·44	45/306·7 (14·7)	16/305·5 (5·2)	2·82 (1·42–5·60)	0·0031
Received blood transfusion	86/134·9	116/132·0	0·66(0·44–0·99)	0·044	144/306·7	201/305·5	0·74 (0·53–1·02)	0·069
Death†	2/113 (1·8%)	3/108 (2·8%)	0·65 (0·11–3·94)	0·64	4/254 (1·6%)	5/249 (2·0%)	0·79 (0·21–2·99)	0·73

IRR=incidence rate ratio. mRDT=malaria rapid diagnostic test. *Negative-binomial models were fitted with a log-time offset, adjusted for the stratification factors site and weight band except models for upper respiratory infection that had no adjusters; dihydroartemisinin–piperaquine versus sulfadoxine–pyrimethamine (reference). †For deaths, the proportion of children who died as a proportion of all children is shown; a logistic regression model was fitted with only the study group as a covariate and a log-time offset, therefore, the relative risk is reported for this outcome.

Table 3: **Association between treatment groups and efficacy outcomes, stratified by age group**

group and 95 participants in the sulfadoxine–pyrimethamine group) initiated hydroxyurea during the study (430 participants in total); 217 (61%) of 357 participants in the sulfadoxine–pyrimethamine group and 213 (58%) of 367 participants in the dihydroartemisinin–piperaquine group. Among participants who took hydroxyurea during the study, the mean duration of administration was 10·0 months (SD 4·7) in the sulfadoxine–pyrimethamine group and 10·5 months (4·7) in the dihydroartemisinin–piperaquine group. After adjustment for duration on hydroxyurea in the model, the incidence of clinical malaria remained lower in the dihydroartemisinin–piperaquine group than the sulfadoxine–pyrimethamine group (IRR 0·20 [95% CI 0·14–0·30]; p<0·0001). Among participants who took hydroxyurea during the study, the incidence of clinical malaria was lower in the dihydroartemisinin–piperaquine than the sulfadoxine–pyrimethamine group (unadjusted IRR 0·098 [95% CI 0·049 –0·198], p<0·0001) and among participants who did not take hydroxyurea during follow-up, the incidence of clinical malaria was also lower in the dihydroartemisinin–piperaquine group than the sulfadoxine–pyrimethamine group (unadjusted IRR 0·319 [95% CI 0·177–0·575], p=0·0001). Statistically significant associations were observed between dihydroartemisinin–piperaquine and hydroxyurea with regard to the incidence of clinical malaria (IRR 0·365 [95% CI 0·153–0·871], $p_{interaction}$=0·0232), hospitalisation admisisons (1·462 [1·082–1·975], $p_{interaction}$=0·0132), and vaso-occlusive crises (1·649 [1·072–2·537], $p_{interaction}$=0·0229).

During the study, mean adherence to in the dihydroartemisinin–piperaquine group was 94·2% compared with 98·7% in the sulfadoxine–pyrimethamine group. No participants reported vomiting in the sulfadoxine–pyrimethamine group after drug administration. Six participants reported ever vomiting in the dihydroartemisinin–piperaquine group, in all cases, only once. No participants reported vomiting after administration of dihydroartemisinin–piperaquine placebo.

Of the 30 participants recruited to the intensive pharmacokinetic substudy, 14 were in the dihydroartemisinin–piperaquine group and 16 participants were in the sulfadoxine–pyrimethamine group. The geometric mean of the weekly area under the curve ($AUC_{0–168h}$) for piperaquine was 5447 ng×h/mL (coefficient of variation 80%), the maximal plasma concentration was

	Dihydroartemisinin–piperaquine (n=367)			Sulfadoxine–pyrimethamine (n=357)			p value*
	Participants, n (%)	Events, n	Incidence per 100 person-years	Participants, n (%)	Events, n	Incidence per 100 person-years	
Urinary tract infection	7 (2%)	7	1·6	8 (2%)	8	1·8	0·79
Stroke	5 (1%)	6	1·4	2 (1%)	2	0·5	0·18
Cellulitis	2 (1%)	2	0·5	2 (1%)	2	0·5	0·99
Diarrhoea	1 (<1%)	1	0·2	3 (1%)	3	0·7	0·37
Constipation	1 (<1%)	1	0·2	2 (1%)	2	0·5	0·62
Soft tissue injury	2 (1%)	2	0·5	1 (<1%)	1	0·2	0·63
Pulmonary tuberculosis	0	0	0	3 (1%)	3	0·7	0·12
Avascular necrosis of femoral head	2 (1%)	2	0·5	0	0	0	0·25
Gastroenteritis	2 (1%)	2	0·5	0	0	0	0·25
Acute bronchiolitis	0	0	0	1 (<1%)	1	0·2	0·50
Varicella	1 (<1%)	1	0·2	0	0	0	0·50
Cholangitis or hepatobiliary disorders	1 (<1%)	1	0·2	0	0	0	0·50
Dermatitis	0	0	0	1 (<1%)	1	0·2	0·50
Epidural haematoma	1 (<1%)	1	0·2	0	0	0	0·50
Febrile seizures	0	0	0	1 (<1%)	1	0·2	0·50
Hypersplenism	1 (<1%)	1	0·2	0	0	0	0·50
Metabolic acidosis	0	0	0	1 (<1%)	1	0·2	0·41
Oral candidiasis	1 (<1%)	1	0·2	0	0	0	0·50
Splenectomy	0	0	0	1 (<1%)	1	0·2	0·50
Spontaneous abortion	1 (<1%)	1	0·2	0	0	0	0·50
Subdural haematoma	1 (<1%)	2	0·5	0	0	0	0·25
Acute severe asthma	1 (<1%)	1	0·2	0	0	0	0·50
Acute gastroenteritis	0	0	0	1 (<1%)	1	0·2	0·50
Transient ischemic attack	1 (<1%)	1	0·2	0	0	0	0·50

p values are for the two-sided test for the difference in incidence of serious adverse events between groups (unadjusted). Adverse events were coded according to the Medical Dictionary for Regulatory Activities. *Fisher's exact test.

Table 4: **Incidence of adverse and severe adverse events**

288 ng/mL (coefficient of variation 79%), and the median time to T_{max} was 3·0 h (range 1·0–6·1).

192 participants were enrolled in the sparse pharmacokinetic and cardiotoxicity substudy; 99 from the dihydroartemisinin–piperaquine group and 93 from the monthly sulfadoxine–pyrimethamine group. Overall, the mean increase in QTc prolongation 4 h after dosing was 8·0 ms (SD 21·7) in the dihydroartemisinin–piperaquine group and –3·9 ms (16·8) in the sulfadoxine–pyrimethamine group: mean difference 11·9 ms (95% CI 8·19–15·6; p<0·0001; appendix 5 p 4). Over 12 months, QT prolongation increased by a mean of 5·2 ms in the dihydroartemisinin–piperaquine group, but this difference was not statistically significant: the mean change in QT interval from baseline to 4 h after each dose at month 0 (first course) and at months 4, 6, 8, and 12 were 7·1 ms (SD 14·5), 3·9 ms (26·0), 8·3 ms (20·1), 14·1 ms (22·2), and 12·3 ms (16·8), respectively (appendix 5 p 3). 12 (12%) of 99 participants in the dihydroartemisinin–piperaquine group and five (5%) of 93 participants in the sulfadoxine–pyrimethamine group had QTc values higher than 450 ms, and none had a QTc value exceeding 480 ms. QTc prolongation of more than 60 ms was observed in two (2%) of 99 children in the dihydroartemisinin–piperaquine group and none in the sulfadoxine–pyrimethamine group. All QTc prolongation was asymptomatic.

Overall, the number and incidence of adverse events and serious adverse events in the two groups were similar (table 4), including the incidence of sickle cell complications or crises. Six (2%) of 367 participants in the dihydroartemisinin–piperaquine group and two (1%) of 357 participants in the sulfadoxine–pyrimethamine group had a stroke or transient ischaemic attack. 14 participants died (six [2%] of 367 participants in the dihydroartemisinin–piperaquine group *vs* eight [2%] of 357 participants in the sulfadoxine–pyrimethamine group), all due to either acute sickle cell anaemia complications (two with stroke [n=2], haemolytic crisis or severe anaemia [n=7], intracranial bleed [n=1], post-surgery death [n=1], and 1 severe vaso-occlusive crisis [n=1]) or lower respiratory tract events (n=2). Six of the seven participants with haemolytic crisis or deaths due to severe anaemia were in the sulfadoxine–pyrimethamine group.

Bacterial growth was obtained in 22 of 511 blood cultures, including 13 contaminants and nine pathogenic

bacteria (five in children aged <5 years and four in children aged ≥5 years): *Escherichia coli* (n=4), *Klebsiella pneumoniae* (n=1), *Streptococcus pyogenes* (n=1), *Staphylococcus aureus* (n=2), and *Enterococcus faecalis* (n=1). Two of the nine pathogenic bacteria were isolated from participants in the sulfadoxine–pyrimethamine group, and seven participants in the dihydroartemisinin–piperaquine group. All nine pathogenic bacterial cultures had extensive high-grade drug resistance, with five showing resistance to cephalosporins. The enterococcal and staphylococcal isolates were both methicillin resistant. Details of the bacterial cultures will be reported separately.

Discussion

In this study, we found that weekly dihydroartemisinin–piperaquine was safe and well tolerated. Compared with participants in the sulfadoxine–pyrimethamine group, the incidence of clinical malaria was 80% lower, the number of malaria-related hospital admissions was 71% lower, and the number of blood transfusions was 30% lower in the dihydroartemisinin–piperaquine group. Our findings suggests that in areas with high antifolate resistance of *P falciparum*, weekly dihydroartemisinin–piperaquine is considerably more effective in reducing the incidence of clinical malaria than the standard of care with monthly sulfadoxine–pyrimethamine with no major safety concerns identified and could be considered for children younger than 5 years who receive concomitant penicillin. However, among children aged 5 years or older who were not receiving penicillin as part of the standard of care, the incidence of non-malaria illnesses was lower in the sulfadoxine–pyrimethamine group than the dihydroartemisinin–piperaquine group, possibly reflecting malaria-independent effects of sulfadoxine–pyrimethamine.

Worldwide, more than 7·7 million people have sickle cell anaemia with an additional 515 000 people diagnosed annually; more than 80% of these individuals reside in the malaria-endemic areas of sub-Saharan Africa. It is estimated that globally, sickle cell anaemia ranks as the 12th leading cause of death in children younger than 5 years.[1] Our results show that malaria infections frequently led to severe outcomes in children with sickle cell anaemia, with more than 50% of all malaria episodes requiring in-patient care, highlighting the particular susceptibility of children with sickle cell anaemia for severe malaria.

There were no differences by sex. The age-specific incidence of malaria in the sulfadoxine–pyrimethamine group was similar in children younger than 5 years when compared with those aged 5–15 years (49·2 *vs* 41·2 events per 100 person-years of observation), suggesting that malaria chemoprophylaxis continues to be needed in these older children, and possibly beyond 15 years of age. Uncomplicated malaria mostly presented as a non-specific febrile illness. Although a marked reduction in malaria events was observed with dihydroartemisinin–piperaquine compared with sulfadoxine–pyrimethamine, no reduction in vaso-occlusive crises was observed, which are often assumed to be triggered by malaria. We hypothesise that febrile events, regardless of aetiology (malarial or non-malarial), are key triggers for sickle cell anaemia vaso-occlusive crises. Although no effect was observed with regard to incidence of vaso-occlusive crises, a significant reduction in the need for blood transfusions was observed in the dihydroartemisinin–piperaquine group, which is consistent with evidence that malaria exacerbates anaemia in people with sickle cell disease.[17] Abnormal splenic function in sickle cell anaemia hinders the clearance of parasitised cells, resulting in continued haemolysis and worsening anaemia. Children with sickle cell anaemia with acute malaria are also prone to dehydration because of reduced fluid intake, increased fluid losses due to vomiting, and insensible water losses, which might precipitate vaso-occlusive crises. Considering the scarcity of safe blood products and transfusion-associated risks in sub-Saharan Africa, utilising dihydroartemisinin–piperaquine for malaria chemoprevention in children with sickle cell anaemia could potentially conserve limited health-care resources and reduce malaria-related severe morbidity and mortality in patients.

Consistent with previous studies that have shown that of hydroxyurea significantly reduces malaria incidence,[18,19] our study also demonstrated the additional benefits of hydroxyurea on malaria incidence. Among participants taking hydroxyurea, the incidence of malaria was 90·2% lower in the dihydroartemisinin–piperaquine group than the sulfadoxine–pyrimethamine group. Among participants who did not take hydroxyurea, the incidence of malaria was 68·1% lower in the dihydroartemisinin–piperaquine group than the sulfadoxine–pyrimethamine group. The beneficial effects of hydroxyurea extended to reduced hospital admissions and vaso-occlusive crises.

Self-reported adherence to weekly dihydroartemisinin–piperaquine or dihydroartemisinin–piperaquine placebo was 95%. Since dihydroartemisinin–piperaquine can cause QT prolongation, nested cardiac monitoring was completed in 99 participants. The corrected QT interval prolongation was greater in the dihydroartemisinin–piperaquine group (mean change 8 ms) than the sulfadoxine–pyrimethamine group (mean change –4 ms; p<0·0001). However, no participants had QTc values higher than 480 ms, and no episodes of QTc prolongation were associated with arrhythmias or adverse clinical events. The 8 ms prolongation with the once-weekly regimen of dihydroartemisinin–piperaquine, which corresponds to the administration of a third of the standard 3-day treatment regimen, was substantially shorter than the 20–30 ms QTc interval prolongation observed with full treatment courses of

dihydroartemisinin–piperaquine when administered for case management of acute malaria or as monthly malaria chemoprevention. None of these monthly regimens have shown evidence of cardiotoxicity.[9] The pro-arrhythmic potential of piperaquine in vitro seems to be lower than that of chloroquine and similar to that of artemether–lumefantrine.[20] The WHO Malaria Policy Advisory Committee also concluded that dihydroartemisinin–piperaquine has a low risk of cardiotoxicity similar to other antimalarials, including quinine, chloroquine, and amodiaquine.[21] Combined with our findings, these data indicate that weekly dihydroartemisinin–piperaquine can safely be considered for malaria prophylaxis in children with sickle cell anaemia.

Of interest, however, is the lower burden of non-malaria illnesses in the sulfadoxine–pyrimethamine group than the dihydroartemisinin–piperaquine group, especially lower respiratory tract events such as pneumonia and acute chest syndrome, which might reflect the malaria-independent effects of sulfadoxine–pyrimethamine, including its broad-spectrum antibiotic effects. This effect was particularly evident in children aged 5 years or older, possibly because of the absence of antibiotic prophylaxis in this age group. Current sickle cell anaemia guidelines in the region recommend that only children younger than 5 years should receive penicillin-V prophylaxis. Extending the age range for prophylaxis with penicillin-V to children 5 years or older or trials that combine weekly dihydroartemisinin–piperaquine with daily penicillin or other antibiotics compared with weekly dihydroartemisinin–piperaquine alone should be considered. Also, the numerically higher incidence of stroke or transient ischemic attacks in children in the weekly dihydroartemisinin–piperaquine group (n=6) compared with children in the monthly sulfadoxine–pyrimethamine group (n=2) might warrant further investigation although the association was not statistically significant.

Widespread use of dihydroartemisinin–piperaquine for malaria chemoprevention might raise concern about potential emergence and spread of drug resistance, especially if dihydroartemisinin–piperaquine is also used for case-management. Although children with sickle cell anaemia represent a relatively small proportion of the population, and the corresponding selective drug pressure on the parasite population is expected to be small, the updated 2022 WHO recommendations for malaria chemoprevention[22] are likely to lead to increased consideration of dihydroartemisinin–piperaquine for various other indications, including for the prevention of malaria in pregnant women living with HIV,[23,24] post-discharge malaria chemoprevention,[25] perennial malaria chemoprevention,[26] and intermittent preventive treatment in school children.[27,28] Close monitoring and surveillance are essential to assess the impact of widespread dihydroartemisinin–piperaquine use for chemoprevention on parasite resistance to artemisinins and piperaquine. An economic evaluation will also be important to weigh the enhanced malaria efficacy and reduction in blood transfusions associated with dihydroartemisinin–piperaquine against its lower efficacy on non-malaria infections. Although our data support weekly dosing, monthly dihydroartemisinin–piperaquine could also be considered. Further research comparing long-term safety and adherence of monthly regimens would inform optimal dosing strategies for this lifelong intervention.

Key strengths of this study include its placebo-controlled design, which minimises assessment bias through effective masking of participants, caregivers, and study staff. The high follow-up rate (96%) and high proportion of children contributing to the primary endpoint, with a median of 14·7 months (IQR 11·2–18·2) of follow-up, enhances internal validity. Additionally, the multi-centre design across two countries increases result generalisability.

This study also had limitations. First, only the first intervention dose was directly observed, with subsequent doses administered at home. The high self-reported adherence might reflect social desirability bias and likely overestimate true and real-world adherence. Second, the study had multiple secondary endpoints without multiplicity adjustment, which increases the risk of type I errors. Third, although the study was adequately powered for the primary malaria endpoint, the study was not powered to definitively assess effect modification by subgroups and for some clinically relevant adverse outcomes. Fourth, the study was not designed to fully assess the potential antimicrobial effects of sulfadoxine–pyrimethamine and the differences between children younger than 5 years and those 5 years and older.

These findings provide evidence for policy makers in countries with a high burden of sickle cell anaemia and high levels of *P falciparum* antifolate resistance to consider transitioning from monthly sulfadoxine–pyrimethamine to weekly dihydroartemisinin–piperaquine for malaria chemoprevention in children younger than 5 years with sickle cell anaemia who also receive penicillin-V prophylaxis. For older children, however, replacing sulfadoxine–pyrimethamine with dihydroartemisinin–piperaquine should only be considered after further studies (eg, malaria chemoprophylaxis with concurrent antibiotics [extending penicillin-V prophylaxis beyond 5 years, azithromycin, or cotrimoxazole]). In areas with lower levels of *P falciparum* sulfadoxine–pyrimethamine resistance, as observed in most of west Africa, the relative benefits of dihydroartemisinin–piperaquine over sulfadoxine–pyrimethamine might be less pronounced as sulfadoxine–pyrimethamine has retained effectiveness for malaria chemoprevention and provides non-malarial (eg, anti-microbial) benefits. Policy makers should carefully evaluate local resistance patterns and consider both effects

when deciding on optimal chemoprevention strategies for children with sickle cell anaemia.

Contributors

RI, KP, FtK, RO, CCJ, and BR conceived the study and obtained funding and, together with TG, JR, JMS, KD, PD, RW, and JT designed the study. TG, RK, NP, WN, CK, PA, LT, JK, DK, MI, JT, and ET obtained the data, including participant assessment and laboratory testing. PA and TG conducted project administration. JMS, KD, MI, TG, and RI curated the data and conducted data analysis. RI, JMS and FtK wrote the original draft, and all authors critically reviewed the manuscript. All authors had access to all the data in the study and RI, KP, FtK, and BR had final responsibility for the decision to submit for publication. All authors have seen and approved of the final text of the manuscript.

Declaration of interests

The Mahidol-Oxford Tropical Medicine Research laboratory, which tested our pharmacokinetic samples, previously did similar paid work for Fosun Pharma (Shanghai, China). RI and JT received travel expenses to attend meetings from Fosun Pharma. All other authors declare no competing interests.

Data sharing

De-identified participant data and the data dictionary will be made available on a public repository after the publication of secondary outcome data and will be accessible on request from the corresponding author, with an approved study proposal and a signed data access agreement.

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