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Intermittent preventive treatment with dihydroartemisinin-piperaquine in young Ugandan children and risk of malaria following cessation: A randomised controlled trial

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Contributors

DH, MF, GD, and MK conceived of the study with input from MM, PJ, AK, TC, TR, and EC. MM, AK, TC, and GD developed the procedures and wrote the protocol. MM and AK coordinated the fieldwork with input from GD and MK. PO coordinated the laboratory work with input from PJ. BO and NN provided supervision of the study pharmacy, and JO supervised data management. PJ and GD performed the statistical analysis with input from MM, AK, and MK. All authors reviewed the protocol and gave permission for publication.

Conflicts of Interests

We declare that we have no competing interests.

Data Sharing Statement

Data collected for the study including individual participant data and data dictionaries defining fields in the datasets have been made available to others through request to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub (DASH): https://dash.nichd.nih.gov/Resource/Tutorial. Data available include de-identified individual level screening and enrollment data, individual participant data, repeated measures during childhood, repeated doses for vomiting, and corresponding data dictionaries. Related study documents made available include the study protocol, statistical analysis plan, case report forms, and informed consent documents. Data can be accessed through the NICHD-DASH website (https://dash.nichd.nih.gov) following user registration and a research data request process. The NICHD DASH Data Access Committee reviews all requests to determine that a requester's proposed use of the data is scientifically and ethically appropriate and does not conflict with constraints or informed consent limitations identified by the institutions that submitted the data.

Trial registration

This trial is registered at ClinicalTrials.gov ()

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Summary

Background.—Intermittent preventive treatment of malaria (IPT) with dihydroartemisinin-piperaquine (DP) is a promising strategy for malaria prevention in young African children. However, the optimal dosing strategy is unclear and there are conflicting results regarding the risk of malaria following cessation of chemoprevention.

Methods.—We conducted a double-blind, randomised controlled trial of IPT with DP every 4 weeks versus every 12 weeks in a historically high transmission district of Uganda. Children received study drugs from 8 weeks to 24 months of age and followed to 36 months of age. The primary outcome was the incidence of symptomatic malaria. Analyses were modified intention to treat and adjusted for potential confounders (maternal gravidity, maternal parasitemia status at enrollment).

Findings.—Between October 2014 and May 2015, 191 children were born, and 183 children reached 8 weeks of age and assigned to receive DP every 4 (n=96) or 12 weeks (n=87) and included in the primary analysis. During the intervention, children receiving DP every 4 weeks had a significantly lower incidence of malaria compared to children receiving DP every 12 weeks (0.018 vs 0.39 episodes per person year (ppy), adjusted incident rate ratio (aIRR) 0.041, 95% CI 0.012-0.15, p<0.0001). After stopping IPT, children who previously received DP every 4 weeks had a lower incidence of malaria compared to children who previously received DP every 12 weeks (0.73 vs. 1.1 episodes ppy, aIRR 0.62, 95% CI 0.40-0.95, p=0.028).

Interpretation.—IPT with DP given every 4 weeks was superior to DP given every 12 weeks for the prevention of malaria during childhood, and this protection was extended for up to one year after stopping IPT.

Keywords

malaria; intermittent preventive treatment; dihydroartemisinin-piperaquine

Introduction

Controlling, and ultimately eliminating malaria in high transmission settings such as Uganda remains a major challenge. Partial immunity to malaria develops through repeated exposure, leading first to protection against severe forms of disease, followed by protection against symptomatic illness.[1] Therefore, in highly endemic areas, the burden of malaria is heavily borne by young children. The only widely used tool for the prevention of malaria in African children is long lasting insecticidal bednets (LLIN). However, there is concern for diminishing efficacy of LLIN due to the alarming emergence of vector resistance to pyrethroids.[2] The World Health Organization also recommends indoor residual spraying of insecticides (IRS) as a central part of malaria control policy given its efficacy in reducing vector densities and malaria morbidity [3,4] but coverage rates have been low (<10%), possibly due to costs from spraying with non-pyrethroid insecticides [5]. There remains a

pressing need to optimize currently deployed interventions and to develop innovative strategies to prevent malaria in early childhood.

The use of intermittent preventative treatment (IPT) with antimalarial drugs for African children at high risk for malaria is an effective option in certain settings. In areas with a low prevalence of sulfadoxine-pyrimethamine (SP) resistance, IPT with SP given at the time of routine vaccination in infants (IPTi) has been shown to be safe and effective against malaria in the first year of life [6]. In settings where malaria transmission is highly seasonal, seasonal malaria chemoprevention (SMC) with SP plus amodiaquine has been found to be highly effective and safe[7]. However, neither IPTi nor SMC are recommended in areas with high prevalence of SP resistance and/or perennial malaria transmission like much of Central and East Africa[5]. In these settings, the safe, highly efficacious artemisinin-based combination therapy dihydroartemisinin-piperaquine (DP) has emerged as an excellent candidate for use as IPT in children given its prolonged post-treatment prophylaxis[8-12]. In two studies conducted in the same high transmission setting, IPT with DP given monthly was associated with a 58% protective efficacy among HIV-unexposed children[11], and 69% protective efficacy among HIV-exposed uninfected children[12], compared with no chemoprevention. However, these studies were open-label, and study drugs were not directly observed, leading to high levels of inadequate drug exposure and probable nonadherence. Indeed, among a subset of children with high piperaquine exposure, DP was nearly 100% protective against malaria[13].

Though IPT may be effective in preventing malaria in children, a potential concern is the impact chemoprevention may have on the acquisition of antimalarial immunity and risk of malaria after chemoprevention has stopped. Though some studies have reported that children receiving chemoprevention have an increased risk of symptomatic malaria following cessation compared to children who do not receive chemoprevention (i.e. “rebound” malaria),[14,15] other studies have reported either no rebound [6] or evidence of sustained protection following cessation[16]. In a prior study of IPT with DP given from 6 months to 24 months of age that we conducted in a high transmission setting in Uganda, there was no difference in the per protocol risk of symptomatic malaria between children who had previously received DP every 4 weeks or no chemoprevention in the year following cessation[11]. However, in a post-hoc analysis considering piperaquine exposure during the intervention as a marker of drug adherence, children highly adherent to DP had a 97% reduction in symptomatic malaria during the time the intervention was given[13] and a 55% reduction in symptomatic malaria in the year following cessation in comparison to children given SP[17]. This may be due to improved priming of cellular immune responses[17], as has been observed in several animal and experimental models where parasitemia is suppressed with drugs that are active only against erythrocytic stages.[18-20]

Although IPT with DP is effective at preventing malaria in young children, it is unclear whether the potential greater efficacy of more frequent dosing will outweigh the practical benefits of less frequent dosing. Furthermore, there are conflicting results regarding the risk of malaria following cessation of chemoprevention. We therefore conducted a double-blind randomised controlled trial of IPT with DP every 4 weeks vs every 12 weeks between 8 weeks and 24 months of age, and compared the incidence of malaria both during the

intervention and after cessation from 24-36 months of age. We addressed limitations of previous studies by providing directly observed therapy of the first dose of study drugs.

Methods

Study design and participants

This study describes the second phase of a double-blind, randomised controlled trial of IPT for the prevention of malaria in pregnancy and young children. The study was conducted in Tororo District, Uganda, an area of historically high malaria transmission intensity with perennial transmission from October 2014 through May of 2018. Following a universal LLIN campaign in November 2013, near universal LLIN coverage was reported in Tororo district [4] From December 2014-February 2015, indoor residual spraying (IRS) using the carbamate bendiocarb was initiated in Tororo[4]; subsequent rounds of bendiocarb IRS were conducted in June-July 2015 and November-December 2015. A fourth round of IRS was conducted in June-July 2016 with pyrimiphos-methyl (Actellic), a long-lasting organophosphate, and a fifth round of Actellic was conducted in June-July 2017.

In the first phase of the study, eligible participants were HIV-uninfected women at least 16 years of age with a viable pregnancy between 12-20 weeks confirmed by ultrasound. Participants were required to provide written informed consent, agree to come to the study clinic for any illness, and to avoid medications given outside the study protocol. Women with chronic medical problems or active medical problems requiring inpatient evaluation were excluded. Complete entry criteria are provided (Study Protocol)[21]. In the second phase of the study, children born to these mothers were followed through 36 months of age.

The study was approved by the ethics committees of Makerere University School of Biomedical Sciences, the Uganda National Council for Science and Technology, and the University of California San Francisco. Written informed consent was provided by all study participants.

Randomization and masking

Women and their unborn child(ren) were randomised to one of 4 treatment arms including both the IPT intervention for the woman during pregnancy and her unborn child(ren) in a 1:1:1:1 randomization scheme: 1) women DP every 8 weeks, children DP every 4 weeks, 2) women DP every 4 weeks, children DP every 4 weeks, 3) women DP every 8 weeks, children DP every 12 weeks, and 4) women DP every 4 weeks, children DP every 12 weeks. Children were analyzed as those who received either DP every 4 weeks (groups 1, 2) versus DP every 12 weeks (groups 3,4). Children were assigned to a treatment group at the time their mothers were randomised in the parent study using premade consecutively numbered opaque, sealed envelopes. A randomization list was computer-generated using permuted variable sized blocks of 6 and 12 by a study member not directly involved in the conduct of the study. Pharmacists not otherwise involved in the study were responsible for treatment allocation and preparation of study drugs. Placebos of DP were used such that every 4 weeks, participants received the same number of placebo pills with the same appearance as

their active drug. All study doses were dispensed by a study nurse blinded to the participant's treatment regimen.

Procedures

At birth, children underwent a standardized examination, and given standard neonatal care including immunization, ophthalmic tetracycline, vitamin K and A supplementation. Children received all medical care at a dedicated study clinic open daily.

Children were given study drugs from 8 weeks to 24 months of age. Each treatment of DP consisted of half strength tablets (20mg/160mg tablets [Duo-Cotecxin, Holley-Cotec, Beijing, China]) given once a day for 3 consecutive days according to weight-based guidelines (Study Protocol, Appendix E). Children randomised to DP every 12 weeks received a placebo mimicking the dosing of DP every 4 weeks when they were not receiving active study drugs. Administration of the first daily doses were directly observed in the clinic. The second and third daily doses were administered by the childs' parent/ guardian at home using pre-packaged drugs in opaque envelopes. Parents/guardians were instructed to bring the child to the study clinic in case of vomiting within 30 minutes of drug administration or if study drug was lost.

Routine visits were conducted every 4 weeks, including assessment of adherence to study drugs administered at home and LLIN use, and collection of blood for the detection of parasites. Routine laboratory testing was performed every 16 weeks (for complete blood count and alanine aminotransferase.) Adverse events were assessed and graded according to standardized criteria at every visit to the study clinic [22] Mothers were encouraged to bring their children to the study clinic any time their children were ill. Children who presented with documented fever (tympanic temperature >38.0°C) or history of fever in the previous 24 hours had blood collected for a thick blood smear for detection of malaria parasites. If the smear was positive, the child was diagnosed with symptomatic malaria and treated with artemether-lumefantrine for uncomplicated cases. Episodes of complicated malaria or treatment failures occurring within 14 days of previous treatment were treated with artesunate or quinine according to Uganda treatment guidelines.

Blood smears were stained with 2% Giemsa and read by experienced laboratory technologists. A blood smear was considered to be negative when the examination of 100 high-power fields did not reveal asexual parasites. For quality control, all slides were read by a second microscopist, and a third reader settled any discrepancies. Dried blood spots collected from study participants every 4 weeks were tested for the presence of malaria parasites with the use of a loop-mediated isothermal amplification (LAMP) kit (Eiken Chemical).

Children were followed until they reached 36 months of age. Study participants were prematurely withdrawn from the study for any of the following: 1) inability to be located for >60 days, 2) movement out of the study area, 3) death, 4) withdrawal of informed consent, and 5) inability to comply with study activities.

Outcomes

The primary outcome was the incidence of symptomatic malaria defined as the number of incident episodes per time at risk. An incident episode was defined as a symptomatic malaria episode requiring treatment and not preceded by another episode in the last 14 days. For comparing the incidence of symptomatic malaria during the intervention, the follow-up period 8 weeks to 24 months of age was the time at risk. For comparing the incidence of symptomatic malaria following cessation of study drugs, the follow-up period >24-36 months of age was the time at risk. Secondary outcomes included the prevalence of parasitemia (microscopic and sub-microscopic assessed by LAMP) measured at routine monthly visits, prevalence of anemia (hemoglobin level, <11 g /dl) measured at routine visits every 16 weeks, the incidence of complicated malaria; the incidence of hospitalizations/ deaths; the incidence of non-malarial febrile illness (presentation within 14 days of a prior episode were not considered incident events); and time to malaria from following cessation of study drugs. Measures of safety and tolerability included observed and reported vomiting after the administration of study drugs and the incidence of grade 3 and 4 adverse events from 8 weeks of age to one month after administration of the last dose of study drugs.

Statistical methods

The primary determinant of our target sample size in the complete study in pregnancy and infancy was based on testing the hypothesis that children randomized to DP every 4 weeks would have a lower incidence of symptomatic malaria following cessation of chemoprevention in comparison to children randomized to DP every 12 weeks, since the magnitude of differences for this outcome was expected to be smaller than those anticipated for other outcomes (Study Protocol). During the chemoprevention intervention (8 weeks to 24 months of age), we assumed an incidence of symptomatic malaria of 3-5 episodes per person year (ppy) among children randomised to DP every 12 weeks based on prior data before the implementation of IRS; assuming 5% lost to follow-up per year, we had 80% power to show a 18-23% reduction among children randomised to DP every 4 weeks (2-sided significance level = 0.05). Following cessation of chemoprevention (24-36 months of age), we assumed an incidence of symptomatic malaria of 3-5 episodes ppy among children randomised to DP every 12 weeks; assuming 5% lost to follow-up per year, we had 80% power to show a 16-21% reduction among children randomised to DP every 4 weeks (2-sided significance level = 0.05).

Data were double-entered and verified in Microsoft Access and statistical analyses performed using Stata, version 15. All analyses were done using a modified intention-to-treat approach including all children who reached 8 weeks of age and received at least 1 dose of study drugs. Incident outcomes were compared using negative binomial regression. Prevalence measures were compared using generalised estimating equations with robust standard errors to account for repeated measures within participants. The cumulative risk of developing symptomatic malaria from cessation of study drugs was estimated using the Kaplan–Meier product limit formula, and associations with IPT regimens assessed using a Cox proportional hazards model. The cumulative risk of developing repeated symptomatic malaria following cessation of study drugs was estimated using a within-subject variance-corrected Cox proportional hazards model. In all analyses, estimates were adjusted for

covariates found to be imbalanced between randomization groups; both unadjusted and adjusted results were reported in tables; adjusted estimates are presented in the text and in figures. In all analyses, a two-sided P-value of <0.05 was considered statistically significant.

This trial is registered at ClinicalTrials.gov ().

Role of the funding source

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

Results

From October 2014 through May 2015, 191 children were born to 194 mothers enrolled and followed through delivery (Figure 1). Of these 191 children, 183 children reached 8 weeks of age, started on study drugs and included in the analysis; 96 children received DP every 4 weeks and 87 children received DP every 12 weeks. Mothers of children randomised to DP every 4 weeks were significantly more likely to be primigravid than mothers of children randomised to DP every 12 weeks (45% vs. 23%, P=0.0019) and non-significantly more likely to have parasites detected at enrollment (63% vs 49%, P=0.075, Table 1). Other maternal and birth characteristics were similar between groups (Table 1).

Among the 183 children analyzed, 166 (91%) and 106 (87%) were followed-up to 24 months and 36 months of age, respectively. The overall mean duration of follow-up was 32 months (SD 6.4), and this was not significantly different between arms (P=0.45). At monthly assessments, 99% (6263/6316) reported sleeping under an LLIN the prior evening, without significant differences between the study arms (P=0.27). Between 8 weeks and 24 months of age when study drugs were given, missed visits due to premature study withdrawal occurred for 57 of 2175 (2.6%) potential visits among children randomised to DP every 12 weeks and for 112 of 2400 (4.7%) potential visits among children randomised to DP every 4 weeks. Among children actively followed, study drugs were not given for 9 of 2118 (0.42%) scheduled visits among children randomised to DP every 12 weeks and for 8 of 2288 (0-35%) scheduled visits among children randomised to DP every 4 weeks.

There were no episodes of symptomatic malaria before study drugs were started. Between 8 weeks and 24 months of age, there were 64 episodes of symptomatic malaria (0.20 episodes ppy); 3 among children who received DP every 4 weeks (incidence 0.018 episodes ppy) and 61 among children who received DP every 12 weeks (incidence 0.39 episodes ppy, Table 2). Children who received DP every 4 weeks had a 96% reduction in the incidence of symptomatic malaria compared to children who received DP every 12 weeks (aIRR 0.04, 95% 0.012-0.15, P<0.0001). Only 3 of 96 children (3.1%) who received DP every 4 weeks developed symptomatic malaria versus 29 of 87 (33%) children who received DP every 12 weeks.Similarly, the prevalence of parasitemia detected by microscopy or LAMP was 89% lower among children who received DP every 4 weeks compared to children who received DP every 12 weeks (aPR 0.11, 95% CI 0.052-0.25, P<0.001, Figure 2). There were 5 episodes of complicated malaria; all occurred among children randomised to DP every 12

weeks. The prevalence of anemia and the incidence of non-malarial febrile illnesses were similar between the treatment arms (Table 2). During the intervention, there were 11 hospitalizations and one death, and the incidence of hospitalization or death was not significantly different between the study arms (Table 2). The one death (respiratory failure not due to malaria) occurred in a 5-month old child randomised to DP every 4 weeks.

Overall, the prevalence and incidence of adverse events were low and similar between the two IPT groups (Table 3). Vomiting after the first dose of drug administration occurred more often in children receiving DP every 4 weeks compared to children receiving DP every 12 weeks (4.3% versus 1.6%, P=0.0010). Vomiting after the second and third administration of the study drugs occurred less than 3% with no significant difference between groups. There were 25 grade 3-4 adverse events and 19 serious adverse events; the incidence of adverse events was similar between the two study arms. No grade 3-4 adverse events or serious adverse events were thought to be related to study drugs.

From 24-36 months of age, after cessation of study drugs, there were 145 episodes of symptomatic malaria; 62 among children previously given DP every 4 weeks (incidence 0.73 episodes ppy) and 83 among children previously given DP every 12 weeks (incidence 1.1 episodes ppy) (Table 4). Children who had previously received DP every 4 weeks had a 38% reduction in the incidence of symptomatic malaria compared to children who had received DP every 12 weeks (aIRR 0.62, 95% CI-0.40-0.95, P=0.028). Similarly, children who had previously received DP every 4 weeks had 41% less prevalent parasitemia detected by microscopy or LAMP after cessation of study drugs compared to children who had received DP every 12 weeks (aIRR 0.59, 95% CI-0.40-0.86, P=0.0061, Table 4). Parasitemia peaked just before each round of IRS, though the protective efficacy of DP every 4 weeks was similar both pre- and post- IRS (Figure 2). The hazard of a first symptomatic malaria episode following cessation of study drugs at 24 months of age was non-significantly lower among children who had previously received DP every 4 weeks compared to children who had received DP every 12 weeks (aHR 0.72, 95% CI 0.45-1.1, P=0.17, Figure 3a). However, the hazard of repeated symptomatic malaria following either cessation of study drugs or malaria treatment was significantly lower among children who had previously received DP every 4 weeks compared to children who had received DP every 12 weeks (aHR 0.68, 95% CI 0.48-0.94, P=0.021, Figure 3b). There were 7 episodes of complicated malaria; 4 among children who had previously received DP every 4 weeks and 3 among children who had previously received DP every 12 weeks. The prevalence of anemia and incidence of non-malaria febrile illnesses were similar between the treatment arms (Table 4). Overall there were nine hospitalizations during 24-36 months of age; seven among children who received DP every 4 weeks and two among children who received DP every 12 weeks, and these differences were not statistically significant (Table 4). No deaths were observed from 24-36 months of age.

Discussion

In this double-blinded randomised controlled trial of IPT with DP conducted in the setting of IRS, children had an overall incidence of 0.20 episodes of symptomatic malaria ppy between 8 weeks and 24 months of age. Children given IPT with DP every 4 weeks had 97% less

symptomatic malaria, and 89% less parasitemia, than children who received DP every 12 weeks. Both regimens were safe and well tolerated. Importantly, after discontinuation of study drugs, children who had previously received IPT with DP every 4 weeks had 39% less symptomatic malaria and 42% less parasitemia than children who had previously received DP every 12 weeks. Together, these data suggest that IPT with DP given every 4 weeks in young children is highly protective against malaria, and, rather than resulting in a "rebound" of malaria after stopping IPT, children continue to have sustained protection for up to one year.

Though IPT with antimalarial drugs for infants and children at high risk for malaria has been shown to be safe and effective for prevention of malaria, several issues have prevented its wide-scale deployment. Although IPTi with SP was protective against symptomatic malaria in the early 2000s,[6] since then, antifolate resistance has become widespread, especially in E. Africa[23], limiting its implementation. Similarly, though SMC has been shown to have an overall protective efficacy of 82% against symptomatic malaria in areas of West Africa with highly seasonal malaria,[7] SMC would not be appropriate in most areas of Central and East Africa were transmission is perennial. The high efficacy, safety, and prolonged post-treatment prophylaxis of DP makes it an excellent candidate for use as IPT in areas with perennial transmission and widespread SP resistance. In comparison to SP, DP has been shown to have >90% efficacy against symptomatic malaria and parasitemia when given as IPT during pregnancy[21] and in school children[24]. In the present study, when DP was given as directly observed therapy to young children in the setting of IRS, symptomatic malaria was nearly eliminated among children ages 8 weeks to 24 months of age.

Both DP regimens were safe and well tolerated overall, and there were no grade 3 or 4 adverse events thought to be related to the two dosing strategies of IPT with DP. The risk of vomiting following administration of the first dose of study drugs was higher in children who received IPT with DP every 4 weeks compared to children who received DP every 12 weeks, which is likely due to a higher number of active study drug doses in children who received DP every 4 weeks[25]. No adverse events suggestive of cardiotoxicity were observed for children enrolled in this study, consistent with a recent meta-analysis demonstrating the cardiac safety of DP when used for malaria treatment or prevention[26]. The prevalence of anemia and hospitalizations were also similar in both IPT arms, though this is not surprising given that adverse outcomes due to symptomatic malaria generally occur after multiple repeated episodes.

Another reason that IPT in children has not been widely implemented is because of concerns that decreasing exposure to malaria might delay the development of natural immunity, leading to an increased risk of malaria when the drugs are stopped. Studies from Tanzania and the Gambia reported that children receiving chemoprophylaxis with pyrimethamine plus dapsone had a higher incidence of symptomatic malaria compared to those receiving placebo in the year following the intervention.[14,15] In contrast, one study reported a sustained decrease in symptomatic malaria following cessation of IPTi-SP [16], though this finding was not reproduced in other studies,[6] and we previously reported that "highly adherent" children who had received DP every 4 weeks had evidence of sustained protection in the year following cessation in comparison to children given no chemoprevention[17] Differences in

these findings could be due to varying transmission intensity between studies (e.g., sustained protection may occur in areas of high transmission intensity where recurrent, high-level malaria infection interferes with the development of antimalarial immunity[27].) Alternatively, differences may be due to the protective efficacy or mechanism of action of study drugs and/or dosing strategies (e.g. continuous prophylaxis vs. intermittent therapy which allows for breakthrough parasitemia). In the present study, children who had previously received DP every 4 weeks continued to have less symptomatic malaria and parasitemia after study drugs were stopped than children who had received DP every 12 weeks. Children who had previously received either IPT arm had a similar hazard to first symptomatic malaria episode following cessation of study drugs, though the hazard of multiple episodes was significantly lower among children who had previously received DP every 4 weeks. This suggests that near complete prevention of malaria in young children with DP may lead to the acquisition of partial, but sustained, protection against subsequent infections.

Although mechanisms for this sustained protection are unclear, one possibility is that selective blockade of blood-stage infection with DP may result in a more robust immune response against pre-erythrocytic stage antigens, as has been suggested by experimental vaccination models utilizing radiation or chemo-attenuated sporozoites [20,28,29] Alternatively, recurrent blood-stage parasitemia has been shown to trigger multiple immunoregulatory mechanisms that may interfere with the development of effective antimalarial immunity. Prevention of blood-stage infection through the use of antimalarial chemoprevention may prevent induction of these regulatory responses [17], though precise mechanisms mediating this protection remain to be determined.

Our study had a few limitations, including the absence of a “no chemoprevention” arm which precluded our ability to make comparisons between our two IPT with DP regimens and the current standard of care. However, in the design of this study it was felt to be unethical to withhold IPT with DP given the findings of our prior studies in the same setting. Baseline characteristics were slightly imbalanced, with children randomised to DP every 4 weeks more likely to be born to primigravid mothers who were parasitemic at enrollment. However, as these covariates were associated with a higher risk of malaria in young children, this may have resulted an underestimation of the protective efficacy of DP every 4 weeks. Our findings may not be readily generalizable to other epidemiologic settings, such as areas where IRS has not been implemented or among children born to HIV-infected mothers, although we have previously shown that monthly DP was well-tolerated and associated with a significant reduction in symptomatic malaria in young HIV-exposed children compared with no chemoprevention[12].Only the first dose of study drug was directly observed, and failure to take the two doses administered at home could have differentially affected the treatment arms. However, this was unlikely to have been a significant factor, as any bias would likely be towards the null. Finally, we did not follow-up children beyond age 3 years, thereby limiting our ability to assess further the effect of stopping chemoprevention on symptomatic malaria incidence in older children.

In summary, in this setting, IPT with DP given every 4 weeks in young children was safe, well tolerated and associated with a marked reduction in the burden of malaria compared to DP given every 12 weeks; furthermore, this protection was sustained for one year beyond

cessation of the intervention. These findings add to a growing body of literature indicating that DP should be considered as IPT during childhood in settings with high SP resistance. Future research should include mechanisms of immunity, pooled analyses of existing studies to improve the precision of estimates of protective efficacy against malaria, evaluations of cost-effectiveness, feasibility studies to assess compliance and effectiveness in real world settings, and additional clinical trials in other epidemiologic settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before the study

Intermittent preventative treatment (IPT) with antimalarial drugs is a strategy for the control of malaria in African children, but evidence is lacking for appropriate drugs to use in areas with either perennial transmission or high prevalence of sulfadoxine-pyrimethamine (SP) resistance. Dihydroartemisinin-piperaquine (DP) is an attractive choice for IPT in these settings given its safety, efficacy and long half-life. We searched PubMed for original articles published in English between January 1, 2000 and June 1, 2018, with the term “dihydroartemisinin-piperaquine AND prevention AND childhood” and identified 5 randomised controlled trials evaluating the use of dihydroartemisinin-piperaquine for the prevention of malaria in children younger than 5 years of age. All trials were conducted in Africa. In three trials assessing the use of monthly DP as seasonal malaria chemoprevention conducted in the setting of low SP resistance, DP was found to be similarly efficacious to regimens containing either SP + amodiaquine or SP + piperaquine. Two other trials conducted in a setting of perennial transmission and high SP resistance assessed the use of monthly DP as intermittent preventative therapy as compared to monthly sulfadoxine-pyremethamine, daily trimethoprim-sulfamethoxazole, or no chemoprevention among children 6 months to 2 years of age. In these trials, DP was found to be significantly more efficacious than SP or no chemoprevention, but efficacy appeared to be limited by inadequate drug exposure and/or poor adherence. These latter two trials also assessed the incidence of malaria after cessation of the study and found no evidence of a “rebound” in malaria incidence among children previously given DP. In all trials, DP was found to be as safe and well tolerated.

Added value of this study

To our knowledge, this is the first study to compare different dosing strategies of IPT with DP for the prevention of malaria in young children. This is also the first trial to compare the risk of malaria following cessation of IPT among children previously given directly observed therapy of IPT. In a setting where malaria transmission had been reduced dramatically due to indoor residual spraying of insecticides (IRS), IPT with DP given every 4 weeks was superior to IPT with DP given every 12 weeks for the prevention of malaria from 8 weeks to 2 years of age. Furthermore, this protection was extended for up to one year after stopping IPT. Both regimens were well tolerated and safe.

Implications of all the available evidence

IPT with DP every 4 weeks virtually eliminated malaria in young children and was associated with less malaria for one year after cessation in comparison to IPT with DP given every 12 weeks. DP should be strongly considered for IPT in settings where transmission occurs throughout the year and resistance to SP is high.

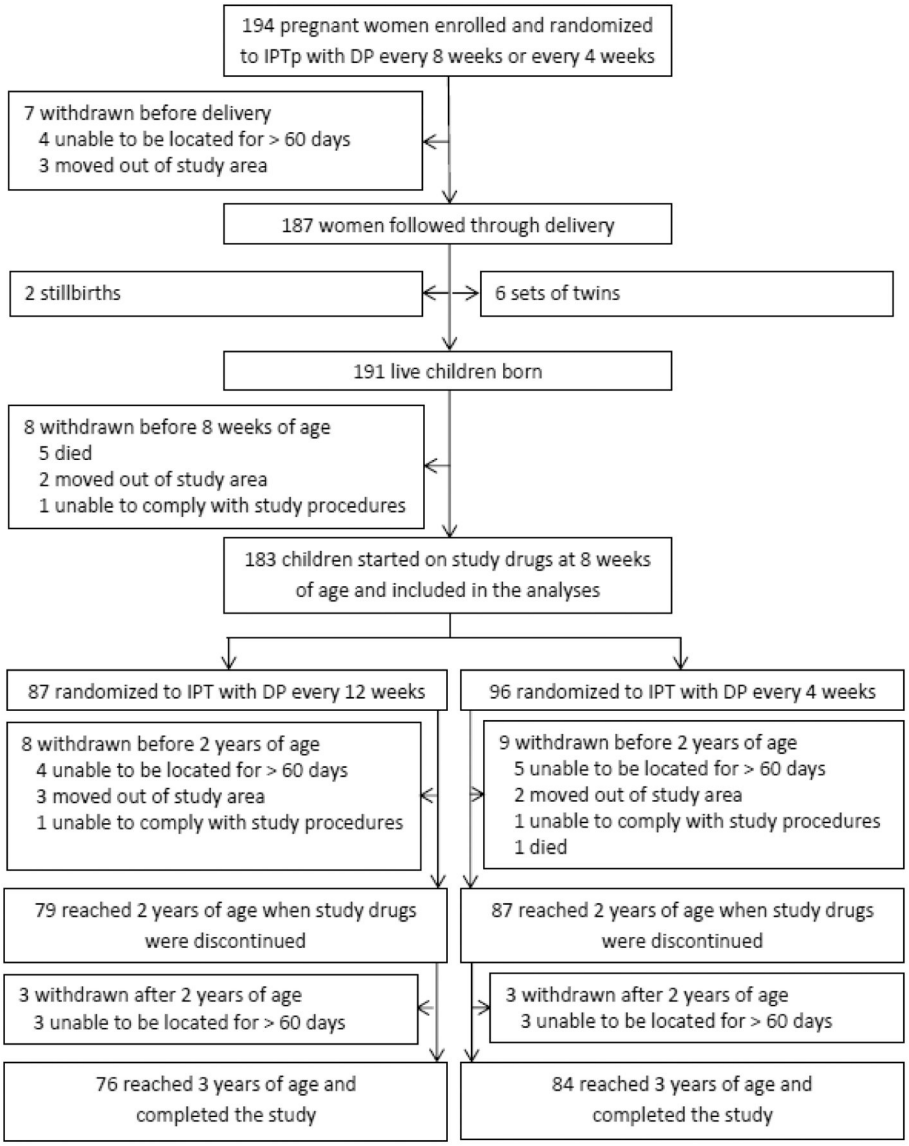

Figure 1. Trial profile.

DP = dihydroartemisinin-piperaquine.

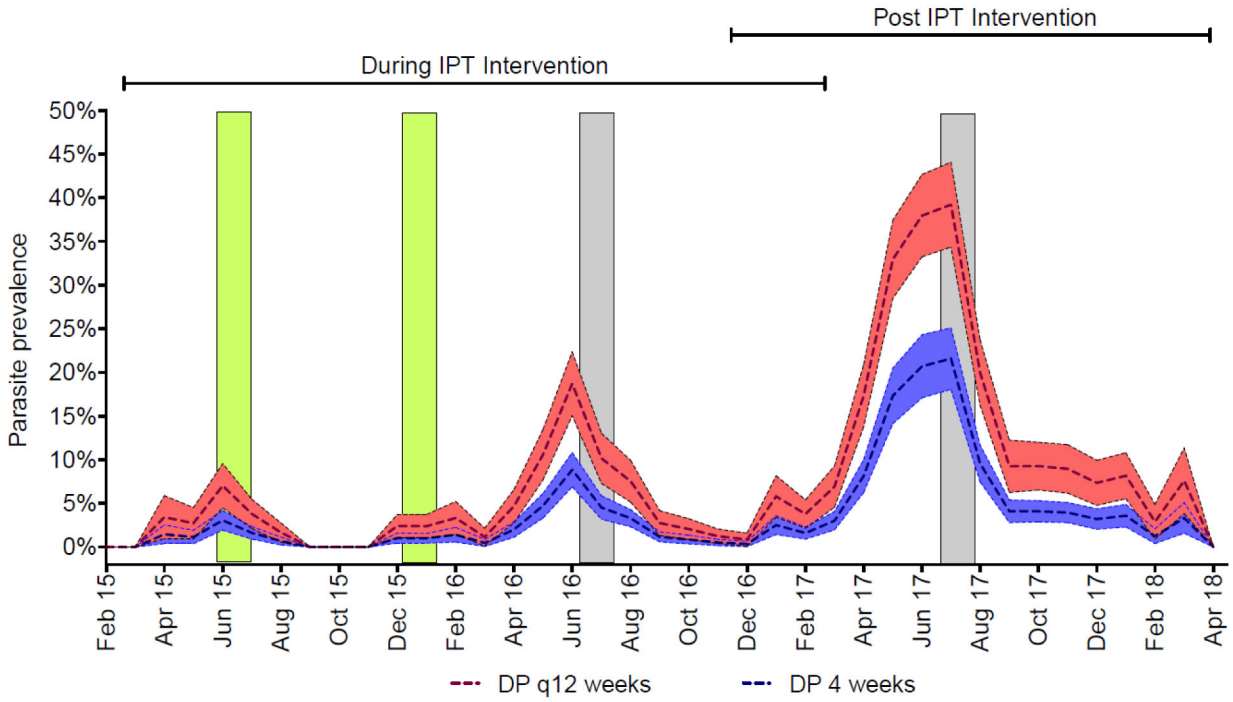

Figure 2. Impact of IPT with DP on parasite prevalence during and post intervention.

Parasite prevalence among children randomized to DP every 4 or 12 weeks both during and post intervention, according to calendar date. Parasite prevalence was assessed monthly by microscopy and loop mediated isothermal amplification (LAMP). Vertical bars represent rounds of indoor residual spraying of insecticides (IRS). Yellow bars represent rounds of IRS with bendiocarb; grey bars represent rounds of IRS with actelic. DP = dihydroartemisinin-piperaquine.

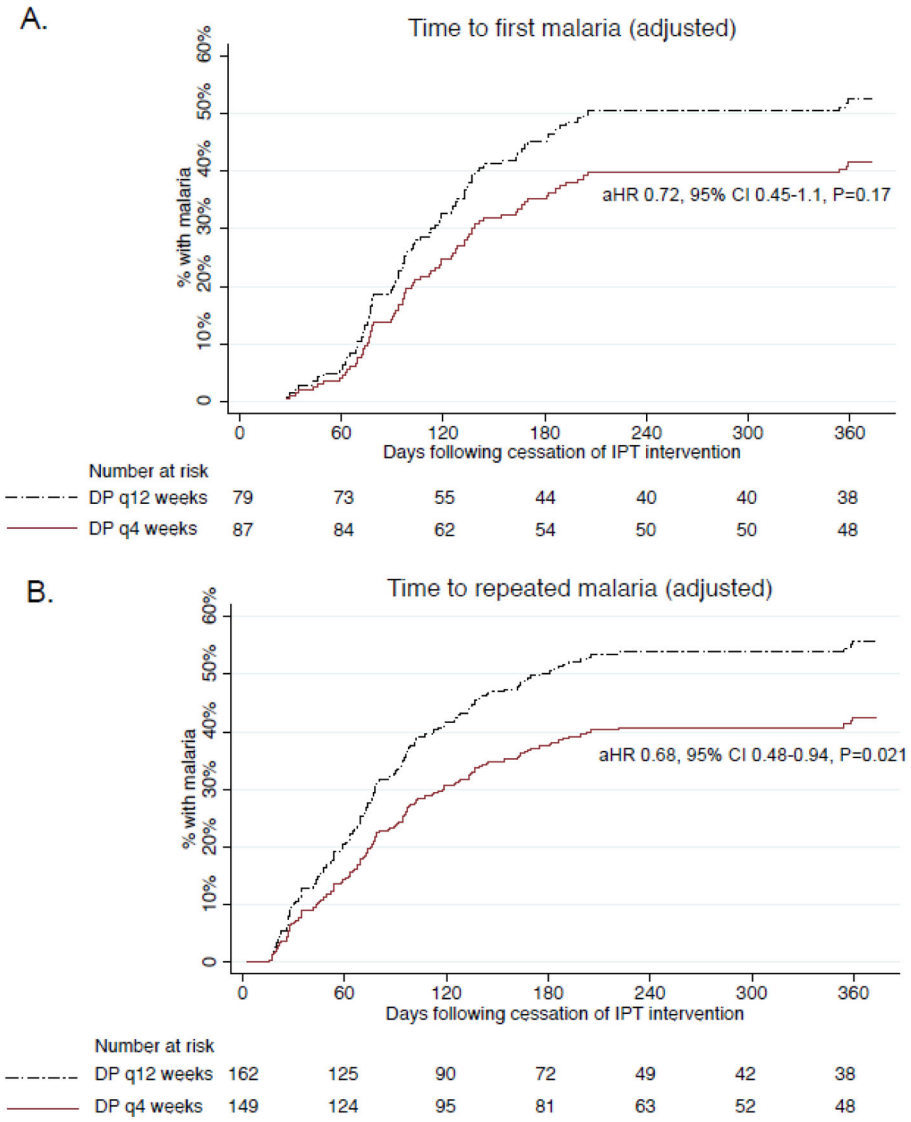

Figure 3. Time to malaria following cessation of IPT intervention.

Time to first episode (**A**) or repeated episodes (**B**) of malaria following cessation of study drugs at 24 months of age. Shown are failure curves and risk tables between IPT groups after adjusting for maternal gravidity and LAMP status at enrolment. DP = dihydroartemisinin-piperaquine.

Table 1.

Characteristics of children stratified by IPT treatment arm

Characteristic	IPT treatment arm	
	DP every 12 weeks (n=87)	DP every 4 weeks (n=96)
Characteristics of mothers at enrollment		
Age in years, mean (SD)	23.1 (4.0)	22.0 (4.4)
Gravidity, n (%)		
1	20 (23%)	43 (45%)
2	30 (35%)	24 (25%)
≥3	37 (43%)	29 (30%)
Household wealth index, n(%)		
Lowest third	25 (29%)	35 (37%)
Middle third	32 (37%)	30 (31%)
Highest third	30 (35%)	31 (32%)
Detection of malaria parasites by LAMP, n (%)	43 (49%)	60 (63%)
Maternal IPTp regimen, n (%)		
DP every 8 weeks	43 (49%)	46 (48%)
DP every 4 weeks	44 (51%)	50 (52%)
Characteristics of children at birth		
Female gender, n (%)	44 (51%)	45 (47%)
Gestational age in weeks at birth, mean (range)	40 (32-42.0)	39 (30-43)
Birth weight in grams, mean (range)	2981 (1320-3840)	2862 (1240-3800)
Placental malaria by microscopy, n/N (%)	1/86 (1.2%)	2/95 (2.1%)
Placental malaria by LAMP [c], n/N (%)	1/86 (1.2%)	6/95 (6.3%)
Placental malaria by histology, n/N (%)	23/86 (27%)	34/95 (36%)

[a] Episodes of malaria per person year at risk

[b] Proportion of routine blood samples positive for malaria parasites by LAMP

[c] Loop amplified isothermal amplification

Table 2.

Protective efficacy of IPT with DP given every 12 weeks vs. every 4 weeks from 8 weeks to 24 months of age

Outcome	Episodes (incidence [a]) or prevalence (%)		Unadjusted		Adjusted [b]	
	DP every 12 weeks [c] n=87	DP every 4 weeks N=96	IRR or PR (95% CI)	p-value	IRR or PR (95% CI)	p-value
Incidence of symptomatic malaria	61 (0.39)	3 (0.018)	0.045 (0.013-0.16)	<0.0001	0.041 (0.012-0.15)	<0.00001
Microscopic parasitemia [d]	69/2021 (3.4%)	3/2186 (0.14%)	0.039 (0.012-0.13)	<0.0001	0.037 (0.01-0.12)	<0.0001
Microscopic or sub-microscopic parasitemia [d]	99/2010 (4.9%)	13/2173 (0.60%)	0.12 (0.053-0.28)	<0.0001	0.11 (0.052-0.25)	<0.0001
Anemia [e]	222/486 (46%)	247/518 (48%)	1.0 (0.87-1.2)	0.65	1.0 (0.86-1.2)	0.79
Incidence of non-malarial febrile illnesses	555 (3.6)	599 (3.6)	1.0 (0.84-1.2)	0.98	1.0 (0.83-1.2)	0.97
Incidence of hospitalization or death	5 (0.032)	7 (0.042)	1.3 (0.39-4.5)	0.65	2.0 (0.58-6.7)	0.27

[a] Per person year at risk

[b] Controlling for maternal gravidity and maternal parasitemia at enrolment

[c] Reference group

[d] Measured at the time of routine visits conducted every 4 weeks, including any episode of malaria diagnosed within the prior 28 days

[e] Hemoglobin < 11 gm/dL at the time of routine visits conducted every 16 weeks

Table 3.

Measures of safety and tolerability

Outcome	IPT treatment arm	
Prevalence measures	**DP every 12 weeks n/N (%)**	**DP every 4 weeks n/N (%)**
Vomiting following administration of study drugs [a]		
Observed after administration of 1st dose in clinic	33/2109 (1.6%)	99/2280 (4.3%) [b]
Reported after administration of 2nd dose at home	40/2102 (1.9%)	65/2270 (2.9%)
Reported after administration of 3rd dose at home	18/2102 (0.9%)	34/2270 (1.5%)
Incidence measures	**Events [c]**	**Events [c]**
Individual adverse events of any severity [d]		
Cough	998 (6.2)	1127 (6.4)
Diarrhea	415 (2.6)	470 (2.7)
Vomiting	108 (0.67)	114 (0.65)
Rash	35 (0.22)	43 (0.25)
Conjunctivitis	25 (0.15)	34 (0.19)
Anorexia	24 (0.15)	18 (0.10)
Malaise	10 (0.064)	10 (0.059)
Individual grade 3-4 adverse events		
Anemia	2 (0.012)	4 (0.023)
Thrombocymiddleenia	2 (0.012)	4 (0.023)
Respiratory distress	1 (0.0064)	1(0.0059)
Elevated alanine aminotransferase	0 (0)	2 (0.011)
Cough	0 (0)	2 (0.011)
Diarrhea	1 (0.0064)	1(0.0059)
Seizures	0 (0)	1(0.0059)
Neutropenia	0 (0)	1(0.0059)
Altered mental status	1 (0.0064)	0 (0)
Dehydration	1 (0.0064)	0 (0)
Malnutrition	0 (0)	1(0.0059)
All grade 3-4 adverse events	8 (0.049)	17 (0.097)
Grade 3-4 adverse events possibly related to study drugs	0 (0)	0 (0)
All serious adverse events	7 (0.043)	12 (0.069)

[a] Including both active study drug and placebo

[b] p=0.001

[c] Number of events (incidence per person year at risk)

[d] Includes only those categories with at least ten total events

Table 4.

Malaria and non-malarial outcomes between 24-36 months of age after IPT discontinued

Outcome	Episodes (incidence [a]) or prevalence (%)		Unadjusted		Adjusted[b]	
	DP every 12 weeks [c] N=79	DP every 4 weeks N=87	IRR or PR (95% CI)	p-value	IRR or PR (95% CI)	p-value
Incidence of symptomatic malaria	83 (1.1)	62 (0.73)	0.70 (0. 46-1.1)	0.088	0.62 (0.40-0.95)	0.028
Microscopic parasitemia [d]	109/1011 (11%)	77/1089 (7.1%)	0.66 (0.46-0.96)	0.030	0.60 (0.41-0.88)	0.0082
Microscopic or sub-microscopic parasitemia [d]	148/996 (15%)	103/1077 (9.6%)	0.65 (0.45-0.95)	0.025	0.59 (0.40-0.86)	0. 0061
Anemia [e]	56/217 (26%)	51/236 (22%)	0.83 (0.55-1.3)	0.38	0.83 (0.55-1.2)	0.36
Incidence of non-malarial febrile illnesses	216 (2.75)	235 (2.77)	1.0 (0.82-1.2)	0.93	1.0 (0.81-1.2)	1.0
Incidence of hospitalization or death	2 (0.025)	7 (0.083)	3.2 (0.67-16)	0.14	4.2 (0.83-21)	0.082

[a] Per person year at risk

[b] Controlling for maternal gravidity and maternal parasitemia at enrolment

[c] Reference group

[d] Measured at the time of routine visits conducted every 4 weeks, including any episode of malaria diagnosed within the prior 28 days

[e] Hemoglobin < 11 gm/dL at the time of routine visits conducted every 16 weeks