Monthly sulfadoxine–pyrimethamine versus dihydroartemisinin–piperaquine for intermittent preventive treatment of malaria in pregnancy: a double-blind, randomised, controlled, superiority trial

Richard Kajubi, Teddy Ochieng, Abel Kakuru, Prasanna Jagannathan, Miriam Nakalembe, Theodore Ruel, Bishop Opira, Harriet Ochokoru, John Ategeka, Patience Nayebare, Tamara D Clark, Diane V Havlir, Moses R Kamya, Grant Dorsey

Lancet 2019; 393: 1428–39

Published Online March 22, 2019 http://dx.doi.org/10.1016/S0140-6736(18)32224-4

See Comment page 1388

Infectious Diseases Research Collaboration, Kampala, Uganda (R Kajubi MBChB, T Ochieng MBChB, A Kakuru MSc, B Opira BPharm, H Ochokoru BS, J Ategeka BS, P Nayebare BS); **Department of Medicine, Stanford University, Stanford, CA, USA** (P Jagannathan MD); **Department of Obstetrics and Gynecology, Makerere University College of Health Sciences, Kampala, Uganda** (M Nakalembe MMed); **Department of Pediatrics, University of California, San Francisco, CA, USA** (T Ruel MD); **Department of Medicine, University of California, San Francisco, CA, USA** (T D Clark MHS, Prof D V Havlir MD, Prof G Dorsey MD); **and School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda** (Prof M R Kamya MMed)

Correspondence to: Prof Grant Dorsey, Zuckerberg San Francisco General Hospital, San Francisco, CA 94110, USA **grant.dorsey@ucsf.edu**

Summary

Background Intermittent treatment with sulfadoxine–pyrimethamine, recommended for prevention of malaria in pregnant women throughout sub-Saharan Africa, is threatened by parasite resistance. We assessed the efficacy and safety of intermittent preventive treatment with dihydroartemisinin–piperaquine as an alternative to sulfadoxine–pyrimethamine.

Methods We did a double-blind, randomised, controlled, superiority trial at one rural site in Uganda with high malaria transmission and sulfadoxine–pyrimethamine resistance. HIV-uninfected pregnant women between 12 and 20 weeks gestation were randomly assigned (1:1) to monthly intermittent preventive treatment during pregnancy with sulfadoxine–pyrimethamine or dihydroartemisinin–piperaquine. The primary endpoint was the risk of a composite adverse birth outcome defined as low birthweight, preterm birth, or small for gestational age in livebirths. Protective efficacy was defined as 1–prevalence ratio or 1–incidence rate ratio. All analyses were done by modified intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02793622.

Findings Between Sept 6, 2016, and May 29, 2017, 782 women were enrolled and randomly assigned to receive sulfadoxine–pyrimethamine (n=391) or dihydroartemisinin–piperaquine (n=391); 666 (85·2%) women who delivered livebirths were included in the primary analysis. There was no significant difference in the risk of our composite adverse birth outcome between the dihydroartemisinin–piperaquine and sulfadoxine–pyrimethamine treatment group (54 [16%] of 337 women *vs* 60 [18%] of 329 women; protective efficacy 12% [95% CI –23 to 37], p=0·45). Both drug regimens were well tolerated, with no significant differences in adverse events between the groups, with the exception of asymptomatic corrected QT interval prolongation, which was significantly higher in the dihydroartemisinin–piperaquine group (mean change 13 ms [SD 23]) than in the sulfadoxine–pyrimethamine group (mean change 0 ms [SD 23]; p<0·0001).

Interpretation Monthly intermittent preventive treatment with dihydroartemisinin–piperaquine was safe but did not lead to significant improvements in birth outcomes compared with sulfadoxine–pyrimethamine.

Funding Eunice Kennedy Shriver National Institute of Child Health and Human Development, and Bill & Melinda Gates Foundation.

Introduction

Malaria in pregnancy remains a daunting challenge in Africa, where approximately 50 million women are at risk for *Plasmodium falciparum* infection during pregnancy each year.[1] Although most women living in endemic areas remain asymptomatic when infected with malaria parasites, these infections are associated with maternal anaemia and adverse birth outcomes, including abortions, stillbirth, preterm birth, low birthweight, and infant mortality.[2] Indeed, malaria in pregnancy is estimated to cause 900 000 low birthweight deliveries and 100 000 infant deaths every year.[3,4] For pregnant women living in malaria endemic areas, the World Health Organization (WHO) recommends the use of long-lasting insecticidal nets and intermittent preventive treatment with sulfadoxine–pyrimethamine to prevent infection with malaria parasites and reduce the risk of adverse birth outcomes. However, there are concerns about diminishing efficacy of these interventions caused by the spread of vector resistance to the pyrethroid insecticides used in long-lasting insecticidal nets and widespread parasite resistance to sulfadoxine–pyrimethamine.[5,6] Therefore, an urgent need exists for new strategies to prevent malaria in pregnancy and improve birth outcomes.

Artemisinin-based combination therapies (ACTs) are now the standard treatment for malaria in Africa; however, data about their use as preventive therapy during pregnancy are scarce. The ACT dihydroartemisinin–piperaquine is an attractive alternative to sulfadoxine–pyrimethamine for intermittent preventive treatment in pregnancy because dihydroartemisinin–piperaquine is highly efficacious in eliminating malaria parasites,

Research in context

Evidence before this study

We searched PubMed for original articles published in English between Jan 1, 2000, and June 1, 2018, with the term "dihydroartemisinin–piperaquine AND prevention AND pregnancy" and identified four randomised controlled trials evaluating the use of dihydroartemisinin–piperaquine for the prevention of malaria in pregnancy. All four trials were done in Africa. One trial compared intermittent preventive treatment in pregnancy with monthly dihydroartemisinin–piperaquine plus daily trimethoprim–sulfamethoxazole and daily trimethoprim–sulfamethoxazole alone in HIV-infected pregnant women. This trial was only relevant in terms of safety assessment for this review. Two trials included a group where women were screened for malaria with rapid diagnostic tests at regular intervals and only given dihydroartemisinin–piperaquine if the test was positive—a strategy called intermittent screening and treatment in pregnancy. In both trials, intermittent screening and treatment in pregnancy with dihydroartemisinin–piperaquine was not superior to intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine, and was inferior for some outcomes. Two trials compared intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine versus sulfadoxine–pyrimethamine. In one trial, both drugs were given every 4–6 weeks. In the other trial, sulfadoxine–pyrimethamine was given every 8 weeks and dihydroartemisinin–piperaquine was given every 4 weeks or every 8 weeks. In both trials, intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine was found to be superior to treatment sulfadoxine–pyrimethamine for the prevention of malaria during pregnancy and at delivery; however, there were no differences in the risk of low birthweight or preterm birth. In all four trials, dihydroartemisinin–piperaquine was found to be as safe and well tolerated as the control group, although only two trials included electrocardiography measurements for the evaluation of corrected QT (QTc) interval prolongation in a subset of women.

Added value of this study

This study is the first to compare intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine versus sulfadoxine–pyrimethamine where both drugs are given every 4 weeks, in accordance with the last recommendations from the World Health Organization. This is also the first study powered to detect a difference in birth outcomes and include assessment of QTc prolongation in all women.

Implications of all the available evidence

Our findings show that intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine was superior to intermittent preventive treatment with sulfadoxine–pyrimethamine for the prevention of malaria during pregnancy in a high transmission area where resistance to sulfadoxine–pyrimethamine is widespread. However, there were no significant differences in the risks of adverse birth outcomes, including low birthweight and preterm birth. Both drugs were safe and well tolerated. Intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine holds promise as an alternative to intermittent preventive treatment with sulfadoxine–pyrimethamine ; further studies are needed to determine its role in policy and whether alternative regimens can improve birth outcomes compared with these regimens.

and the long half-life of piperaquine provides at least 4 weeks of post-treatment prophylaxis.[7,8] Two recent studies from east Africa[9,10] showed that intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine was more effective than sulfadoxine–pyrimethamine at reducing the risk of malaria during pregnancy and the risk of placental malaria at delivery.[9,10] However, these studies were not powered to detect differences in adverse birth outcomes, and sulfadoxine–pyrimethamine was dosed less frequently than the current recommendation, which advocates monthly dosing.[11] In 2015, a WHO Malaria Policy Advisory Committee concluded that intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine merits further study, but that sulfadoxine–pyrimethamine should remain the recommended drug for intermittent preventive treatment in pregnancy until there is conclusive evidence that alternative regimens are safe and improve birth outcomes.[11]

In this report, we compare the efficacy and safety of intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine versus dihydroartemisinin–piperaquine in an area of Uganda characterised by intense malaria transmission and a high prevalence of sulfadoxine–pyrimethamine resistance. In our study design, we addressed some of the limitations of previous studies by dosing both regimens once a month, using a composite measure of adverse birth outcomes as the primary outcome, and rigorously assessing safety, including repeated electrocardiography (ECG) measurements for the evaluation of corrected QT (QTc) interval prolongation.

Methods

Study design and participants

This double-blind, randomised trial was done in Busia District, an area in southeastern Uganda that borders Kenya and Lake Victoria, where malaria transmission is perennial and intense. Eligible participants were HIV-uninfected women at least 16 years of age with a viable pregnancy between 12 and 20 weeks gestation confirmed by ultrasound. Participants were required to provide written informed consent, agree to come to the study clinic for any febrile episode or other illness, to avoid medications given outside the study protocol, and plan to deliver in the hospital. Women with a history of serious

adverse events to sulfadoxine–pyrimethamine or dihydroartemisinin–piperaquine, early or active labour, chronic medical conditions or active medical problems requiring inpatient evaluation, or previous antimalarial therapy during this pregnancy were excluded.

The study was approved by the ethics committees of Makerere University School of Biomedical Sciences (Kampala, Uganda), the Uganda National Council for Science and Technology (Kampala, Uganda), and the University of California San Francisco (San Francisco, CA, USA). All study participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned to receive monthly sulfadoxine–pyrimethamine or monthly dihydroartemisinin–piperaquine for intermittent preventive treatment of malaria in pregnancy. Randomisation was done in a 1:1 ratio in permuted blocks of 4 or 8. A computer-generated randomisation list including consecutive treatment numbers with corresponding random treatment assignments was generated by the study principal investigator (GD). Prior to the onset of the study, a set of sequentially numbered, opaque, sealed envelopes were prepared with the treatment allocation number on the outside and the treatment allocation number on the inside. Study physicians were responsible for enrolling participants. Pharmacists who were not otherwise involved in the study were responsible for treatment allocation and the preparation of study drugs. Placebos of sulfadoxine–pyrimethamine and dihydroartemisinin–piperaquine were used such that every 4 weeks, participants received the same number of placebo pills with the same appearance as their active drug.

Procedures

At enrolment, women received a long-lasting insecticidal net, underwent a standardised routine medical examination, and had blood samples collected. Women received all their medical care at a study clinic that was open every day.

Each dose of sulfadoxine–pyrimethamine (tablets of 500 mg of sulfadoxine and 25 mg of pyrimethamine; Kamsidar, Kampala Pharmaceutical Industries, Kampala, Uganda) consisted of three tablets given as a single oral dose once per day on 1 day. Each dose of dihydroartemisinin–piperaquine (tablets of 40 mg of dihydroartemisinin and 320 mg of piperaquine; Duo-Cotexin, Holley-Cotec, Beijing, China) consisted of three tablets given orally once a day for 3 consecutive days. All participants received the active study drugs (either sulfadoxine–pyrimethamine or dihydroartemisinin–piperaquine) every 4 weeks starting at 16 or 20 weeks gestation. Placebos were used such that every 4 weeks participants received either active sulfadoxine–pyrimethamine plus placebo dihydroartemisinin–piperaquine, or placebo sulfadoxine–pyrimethamine plus active dihydroartemisinin–piperaquine. Administration of the first daily doses of study drugs were directly observed in the clinic, and the second and third daily doses were administered at home. Adherence to study drugs administered at home was assessed by patient recall at the time of their next routine visit.

Routine visits were conducted every 4 weeks, including collection of blood for the detection of malaria parasites by microscopy and quantitative PCR (qPCR), and routine laboratory testing every 8 weeks (for complete blood count and alanine aminotransferase). Women were encouraged to come to the clinic any time they felt ill. Those who presented with a documented fever (tympanic temperature ≥38·0°C) or history of fever in the previous 24 h had blood collected for a thick blood smear. If the smear was positive, the patient was diagnosed with malaria and treated with artemether–lumefantrine.

Women were encouraged to deliver their babies at the hospital adjacent to the study clinic. Women delivering at home were visited by study staff at the time of delivery or as soon as possible afterwards. At delivery, a standardised assessment was completed including evaluation for congenital anomalies, birthweight, and collection of biological specimens including placental tissue, placental blood, and maternal blood. Following delivery, women were followed for 6 weeks post partum. Adverse events were assessed and graded according to standardised criteria (National Institutes of Health, Division of AIDS table for grading the severity of adult and paediatric adverse events) at every visit to the study clinic.[12] ECGs were done to assess corrected QT (QTc) intervals using *Fridericia's* formula

$$\left(\frac{QT}{\sqrt[3]{RR}}\right)$$

in all women just prior to their first daily dose of study drugs and 3–4 h after their third daily dose of study drugs at 20, 28, and 36 weeks gestation.

Blood smears were collected at enrolment, at each routine visit, and from febrile participants during pregnancy, and from maternal and placental blood at delivery. Blood smears were stained with 2% Giemsa and read by experienced microscopists. A blood smear was considered negative when the examination of 100 high power fields did not reveal the presence of asexual parasites. For quality control, all slides were read by a second microscopist and a third reviewer would settle any discrepant readings. Blood samples collected at enrolment and at the time of each routine visit that were negative by microscopy were tested for the presence of submicroscopic parasitaemia using a highly sensitive qPCR assay targeting the multicopy conserved *var* gene acidic terminal sequence with a lower limit of detection of one parasite per mL of blood.[13] Dried blood spots collected from placental blood were tested for the presence of malaria parasites using a loop-mediated isothermal amplification kit (Eiken Chemical, Tokyo, Japan) as previously described

with a lower limit of detection of ten parasites per mL.[14] Placental tissues were processed for histological evidence of placental malaria as previously described.[15]

Outcomes

The primary outcome was the risk of a composite of adverse birth outcomes, defined as the presence of any of the following among livebirths: low birthweight (<2500 g), preterm birth (<37 weeks), or small for gestational age (<10th percentile relative to an external growth reference).[16] Secondary outcomes were the incidence of symptomatic malaria, the prevalence of parasitaemia by microscopy or qPCR, and the prevalence of anaemia (haemoglobin concentration <10 g/dL) during pregnancy following the administration of the first dose of study drugs; the prevalence of parasitaemia at delivery using microscopy from maternal blood and by both microscopy and loop-mediated isothermal amplification from placental blood; the prevalence of placental malaria based on the presence of any parasites or malaria pigment detected by histopathology; and individual measures of the adverse birth outcomes listed above plus spontaneous abortion (delivery at <28 weeks gestational age), stillbirth (infant born deceased at ≥28 weeks gestational age), neonatal death (infant death within the first 28 days of life), and a composite of any fetal or neonatal death. Additionally, we did a post-hoc analysis on our composite adverse birth outcome, low birthweight, preterm birth, small for gestational age, and neonatal death restricted to singleton, livebirths in the absence of any congenital anomalies. In this post-hoc analysis, classification of small for gestational age was defined as less than the 10th percentile relative to an international standard not available at the time our protocol was written.[17] Measures of safety and tolerability were the prevalence of vomiting following the administration of study drugs, changes in QTc intervals following the administration of study drugs, and the incidence of adverse events following the initiation of study drugs through to 6 weeks post partum.

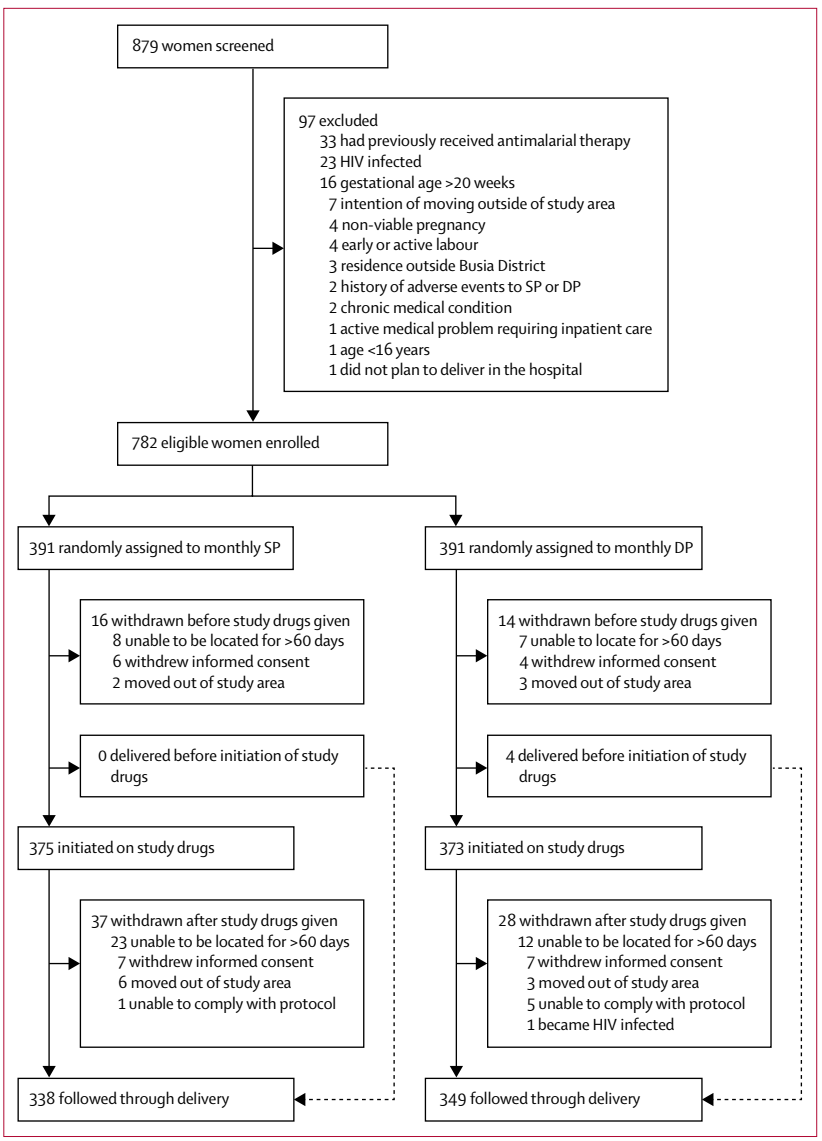

Figure 1: **Trial profile**
DP=dihydroartemisinin–piperaquine. SP=sulfadoxine–pyrimethamine.

Statistical analysis

To test the hypothesis that the use of intermittent preventive treatment in pregnancy with monthly dihydroartemisinin–piperaquine would be associated with a lower risk of our composite adverse birth outcome compared with monthly sulfadoxine–pyrimethamine, we estimated that the risk of this outcome would be 30% in the monthly sulfadoxine–pyrimethamine group based on previous data[10] and calculated that a sample size of 782 (assuming 5% loss to follow-up during pregnancy) would be required for the study to have 80% power to show a 30% lower relative risk with monthly dihydroartemisinin–piperaquine, at a two-sided significance level of 0·05. Statistical analyses were done using Stata, version 14.2. All analyses were done in the modified intention-to-treat population, which included all participants allocated to a treatment group with evaluable outcomes of interest. We did comparisons of simple proportions using the χ^2 test or Fisher's exact test. We did comparisons of proportions with repeated measures using generalised estimating equations, with the use of log-binomial regression and robust standard errors. We did comparisons of incidence measures using a negative binomial regression model. Prevalence ratios were defined as the measures of prevalence in the monthly dihydroartemisinin–piperaquine group divided by the prevalence in the monthly sulfadoxine–pyrimethamine group. Incidence ratios were defined as the incidence of symptomatic malaria in the monthly dihydroartemisinin–piperaquine group divided by the incidence in the monthly sulfadoxine–pyrimethamine group. Point estimates of differences between the treatment groups

	Monthly sulfadoxine–pyrimethamine group (n=391)	Monthly dihydroartemisinin–piperaquine group (n=391)
Age, years	23 (19–27)	23 (19–27)
Gestational age, weeks	15·4 (13·3–17·6)	15·0 (13·4–17·1)
Gestational age category (weeks)		
12–16	234 (60%)	242 (62%)
>16–20	157 (40%)	149 (38%)
Gravidity		
1	102 (26%)	93 (24%)
2	85 (22%)	105 (27%)
≥3	204 (52%)	193 (49%)
ITN coverage		
Ownership of ITN	61 (16%)	50 (13%)
Reported sleeping under an ITN the previous night	48 (12%)	44 (11%)
Haemoglobin concentration (g/dL)	11·5 (1·3)	11·4 (1·2)
Detection of malaria parasites by microscopy	197 (50%)	204 (52%)
Detection of malaria parasites by microscopy or qPCR	326 (83%)	317 (81%)

Data are median (IQR) or n (%). ITN=insecticide-treated net. qPCR=quantitative PCR.

Table 1: **Baseline characteristics**

See Online for appendix

were expressed as the protective efficacy (PE), defined as 1–prevalence ratio or 1–incidence rate ratio. All p values were two-sided, and values less than 0·05 were considered statistically significant.

This trial is registered with ClinicalTrials.gov, number NCT02793622.

Role of the funding source

The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit for publication. RK, AK, PJ, and GD had full access to all the data in the study, and RK, DVH, MRK, and GD had final responsibility for the decision to submit for publication.

Results

Between Sept 6, 2016, and May 29, 2017, 879 women were screened, of whom 782 eligible women were enrolled and randomly assigned to the two treatment groups; 391 to monthly sulfadoxine–pyrimethamine and 391 to monthly dihydroartemisinin–piperaquine (figure 1). Baseline characteristics were similar between the two treatment groups (table 1). Median age at enrollment was 23 years (IQR 19–27), 476 (61%) of 782 women were enrolled at up to 16 weeks gestational age, 195 (25%) were primigravid, 111 (14%) reported owning a long-lasting insecticidal net, and 401 (51%) had malaria parasites detected by microscopy at enrolment. A total of 687 women (88%) were followed through delivery (338 in the sulfadoxine–pyrimethamine group and 349 in the dihydroartemisinin–piperaquine group) and 666 (85%) delivered livebirths. Of the 687 women who gave birth, 68 (10%) delivered at home, with a similar proportion between the sulfadoxine–pyrimethamine (39 [12%]) and dihydroartemisinin–piperaquine (29 [8%]) treatment groups. 13 women gave birth to twins; six of these twin births had dichorionic placentas.

The occurrence of our composite adverse birth outcome did not differ significantly between the treatment groups (54 [16%] of 337 women in the dihydroartemisinin–piperaquine group *vs* 60 [18%] of 329 women in the sulfadoxine–pyrimethamine group; PE 12% [95% CI –23 to 37], p=0·45; table 2). The risks of individual adverse birth outcomes including low birthweight, preterm birth, and small for gestational age did not differ significantly between the treatment groups (table 2). There were a total of 14 spontaneous abortions, seven stillbirths, and ten neonatal deaths, with no significant differences individually or as a composite between the treatment groups (table 2). Notably, four of the 14 spontaneous abortions occurred before the first scheduled dose of study drugs and all of these occurred in women assigned to dihydroartemisinin–piperaquine (figure 1). In a post-hoc analysis restricted to singleton, livebirths in the absence of any congenital anomalies, we noted no significant differences between the two treatment groups in the risks of our composite adverse birth outcome, low birthweight, preterm birth, small for gestational age, and neonatal death (appendix).

By contrast with birth outcomes, we recorded notable differences in malaria-specific outcome measures and maternal anaemia between the treatment groups. After the initiation of study drugs, the incidence of symptomatic malaria during pregnancy was significantly lower in the dihydroartemisinin–piperaquine group than in the sulfadoxine–pyrimethamine group (table 2). The prevalence of parasitaemia at the time of each routine visit was also significantly lower in the dihydroartemisinin–piperaquine group than in the sulfadoxine–pyrimethamine group, both by microscopy alone and by microscopy or qPCR (table 2, figure 2). The risk of maternal anaemia during pregnancy was also significantly lower in the dihydroartemisinin–piperaquine group than in the sulfadoxine–pyrimethamine group (table 2). At delivery, compared with sulfadoxine–pyrimethamine, dihydroartemisinin–piperaquine was associated with a significantly lower prevalence of maternal peripheral parasitaemia, placental parasitaemia by microscopy, or loop-mediated isothermal amplification, and histopathologically confirmed placental malaria (table 2).

In a pre-planned analysis, we also analysed associations between treatment groups and efficacy outcomes for effect modification by gravidity. The prevalence of all malaria-specific outcomes and maternal anaemia were significantly higher in primigravid than in multigravid women (appendix). Adverse birth outcomes were also higher in primigravid women than in multigravid women, but differences were not statistically significant for fetal or neonatal death (p=0·22) or low birthweight

	Monthly sulfadoxine–pyrimethamine group* (n=338)	Monthly dihydroartemisinin–piperaquine group (n=349)	Protective efficacy† (95% CI)	p value
Outcomes assessed at delivery				
Adverse birth outcomes among livebirths				
Composite (primary efficacy outcome)	60/329 (18%)	54/337 (16%)	12% (–23 to 37)	0·45
Low birthweight	29/329 (9%)	24/337 (7%)	19% (–36 to 52)	0·42
Preterm birth	24/329 (7%)	16/337 (5%)	35% (–20 to 65)	0·17
Small for gestational age	41/329 (13%)	39/337 (12%)	7% (–40 to 38)	0·72
Fetal or neonatal death				
Spontaneous abortion	4/338 (1%)	10/349 (3%)	–142% (–665 to 23)	0·13
Stillbirth	5/334 (2%)	2/339 (1%)	61% (–102 to 92)	0·26
Neonatal death	6/329 (2%)	4/337 (1%)	35% (–129 to 81)	0·50
Composite	15/338 (4%)	16/349 (5%)	–3% (–106 to 48)	0·93
Measures of infection with malaria parasites				
Maternal blood positive for malaria parasites by microscopy	28/336 (8%)	1/342 (<1%)	96% (74 to 99)	0·0010
Placental blood positive for malaria parasites by microscopy	28/320 (9%)	1/333 (<1%)	97% (75 to 99)	0·0009
Placental blood positive for malaria parasites by LAMP	70/312 (22%)	7/328 (2%)	90% (80 to 96)	<0·0001
Placental tissue positive for malaria parasites or pigment	197/322 (61%)	94/331 (28%)	54% (44 to 62)	<0·0001
Incidence measures during pregnancy‡				
Symptomatic malaria	75 (0·52)§	3 (0·02)§	96% (88 to 99)	<0·0001
Prevalence measures during pregnancy‡				
Detection of malaria parasites by microscopy	519/1687 (31%)	9/1757 (1%)	98% (96 to 99)	<0·0001
Detection of malaria parasites by microscopy or qPCR	1105/1676 (66%)	369/1746 (21%)	68% (64 to 71)	<0·0001
Anaemia (haemoglobin <10 g/dL)	171/870 (20%)	89/904 (10%)	50% (32 to 73)	<0·0001

LAMP=loop-mediated isothermal amplification. qPCR=quantitative PCR. *Reference group. †Protective efficacy=1–incidence rate ratio or 1–prevalence ratio. ‡Assessed at the time of routine visits following administration of first dose of study drugs. §Number of events (incidence per person-year at risk).

Table 2: **Efficacy outcomes**

(p=0·24; appendix). Considering differences between treatment groups, there was evidence of modification by gravidity for low birthweight ($p_{interaction}$=0·10) and maternal anaemia ($p_{interaction}$=0·01; figure 3). There was no significant difference in the risk of low birthweight in women given dihydroartemisinin–piperaquine compared with those given sulfadoxine–pyrimethamine in primigravid women (4 [6%] of 73 women *vs* 12 [14%] of 84; PE 62% [95% CI –14 to 87], p=0·08) or in multigravid women (20 [8%] of 264 *vs* 17 [7%] of 245; PE –9% [–104 to 41], p=0·78). The prevalence of anaemia was significantly lower in women given dihydroartemisinin–piperaquine than in those given sulfadoxine–pyrimethamine in primigravid women (19 [10%] of 186 routine tests *vs* 80 [36%] of 223 routine tests; PE 72% [95% CI 50–84], p<0·0001) but not in multigravid women (70 [10%] of 718 routine tests *vs* 91 [14%] of 647 tests; PE 30% [–4 to 52], p=0·08).

In our analysis of tolerability and safety outcomes, vomiting occurred in fewer than 0·3% of women after administration of study drugs, with no differences between treatment groups (table 3). The mean change in the QTc interval after administration of study drugs was significantly higher in the dihydroartemisinin–piperaquine group than in the sulfadoxine–pyrimethamine group (table 3). Within the dihydroartemisinin–piperaquine group, the mean change in the QTc interval was greater at 20 weeks gestation (table 3). There were seven events in

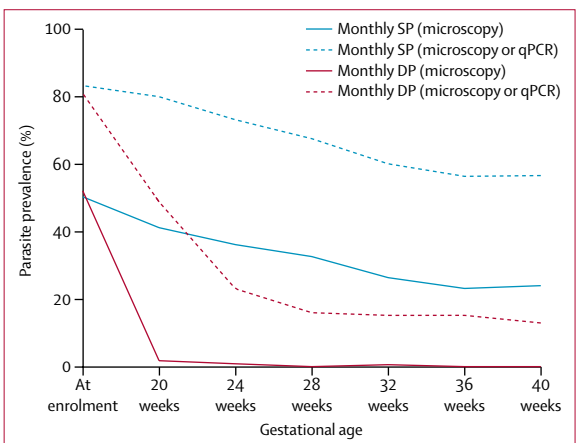

Figure 2: **Parasite prevalence during pregnancy according to week of gestation**
Parasite prevalence was assessed by microscopy and qPCR. Data at 20 weeks gestational age only includes the subset of women who received their first dose of study drugs at 16 weeks gestational age. DP=dihydroartemisinin–piperaquine. qPCR=quantitative PCR. SP=sulfadoxine–pyrimethamine.

which the QTc interval change was greater than 60 ms, and all of these events were in the dihydroartemisinin–piperaquine group. No QTc intervals were greater than 500 ms in either group. No episode of QTc prolongation was associated with arrhythmias, symptoms, or clinical adverse events. The incidence of adverse events of any severity did not differ between the groups (table 3). Of the individual grade 3–4 adverse events, the incidence of congenital anomalies was higher in the dihydroartemisinin–piperaquine group than in the sulfadoxine–pyrimethamine group (table 3). All congenital anomalies observed were regarded as minor and included ten episodes of polydactyly (nine of which were in the dihydroartemisinin–piperaquine group), a club foot (in the sulfadoxine–pyrimethamine group), and one infant born with a cleft palate and club foot (in the

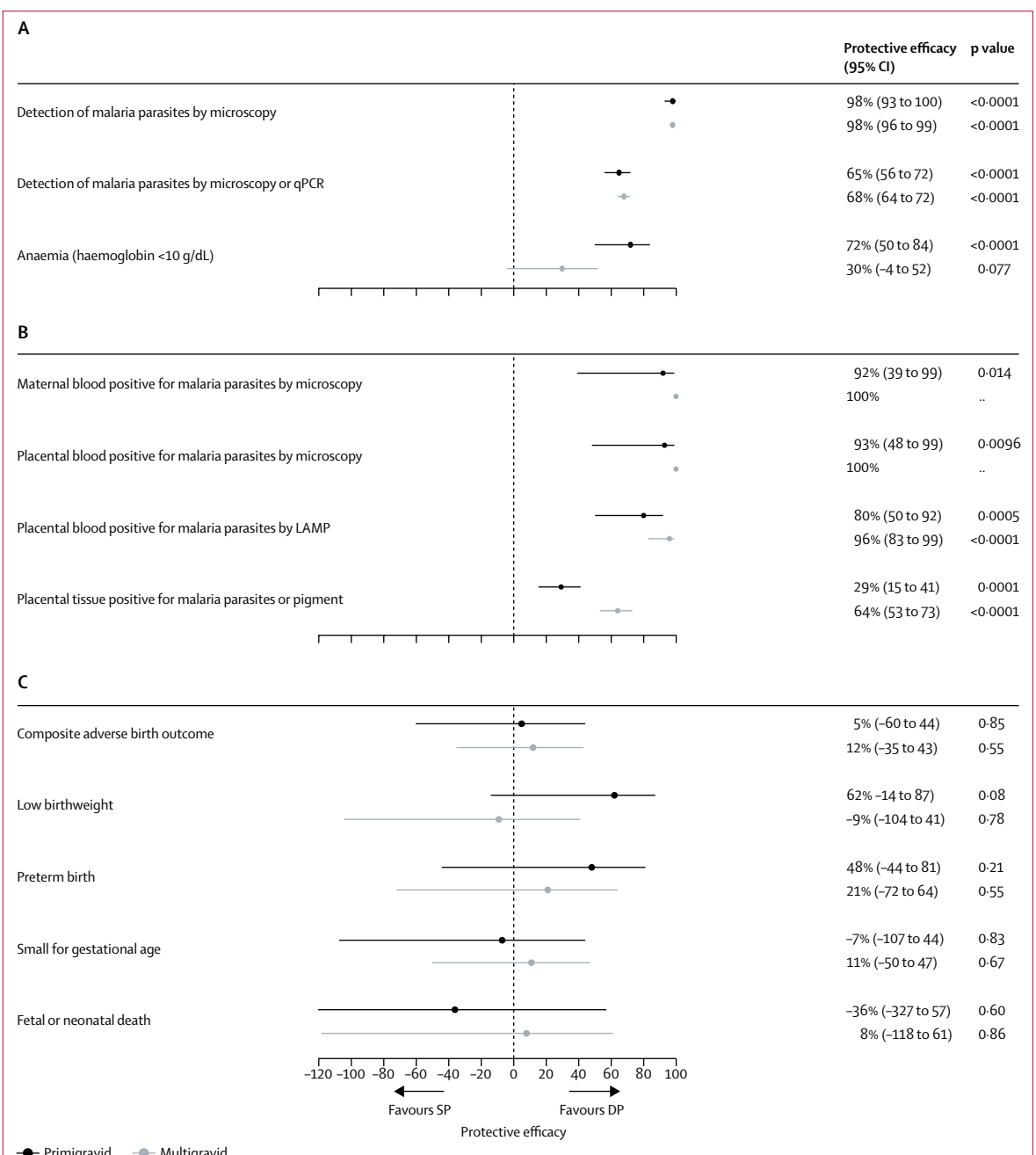

Figure 3: **Protective efficacy of study drugs stratified by gravidity**
(A) Outcomes assessed during pregnancy. (B) Malaria outcomes assessed at delivery. (C) Birth outcomes. DP=dihydroartemisinin–piperaquine. LAMP=loop-mediated isothermal amplification. qPCR=quantitative PCR. SP=sulfadoxine–pyrimethamine.

	Monthly sulfadoxine–pyrimethamine group (n=375)	Monthly dihydroartemisinin–piperaquine group (n=373)	p value
Prevalence measures, n/N (%)			
Vomiting following administration of study drugs*			
Observed after administration of first dose in clinic	1/2057 (<1%)	6/2124 (<1%)	0·10
Reported after administration of second dose at home	1/2057 (<1%)	1/2124 (<1%)	0·98
Reported after administration of third dose at home	0/2057	1/2124 (<1%)	0·51
Continuous measures, mean (SD)			
Change in QTc (following third dose–before first dose), ms			
All measurements (n=2003)	0 (23)	13 (23)	<0·0001
Week 20 gestational age measurements (n=697)	0 (23)	18 (23)	<0·0001
Week 28 gestational age measurements (n=677)	0 (22)	12 (22)	<0·0001
Week 36 gestational age measurements (n=629)	–1 (23)	10 (22)	<0·0001
Incidence measures, events†			
Individual adverse events‡ of any severity§			
Abdominal pain	822 (4·50)	800 (4·22)	0·34
Cough	603 (3·30)	681 (3·59)	0·29
Headache	586 (3·21)	604 (3·19)	0·87
Pyuria	63 (0·34)	69 (0·36)	0·78
Diarrhoea	62 (0·34)	66 (0·35)	0·90
Malaise	54 (0·30)	52 (0·27)	0·72
Vomiting	44 (0·24)	45 (0·24)	0·96
Chills	27 (0·15)	26 (0·14)	0·80
Individual grade 3-4 adverse events‡			
Anaemia	28 (0·153)	8 (0·042)	0·0013
Proteinuria	10 (0·055)	6 (0·032)	0·29
Congenital anomaly	2 (0·011)	10 (0·053)	0·042
Thrombocytopenia	7 (0·038)	3 (0·016)	0·20
QTc interval prolongation	0 (0)	9 (0·047)	0·0037
Stillbirth	5 (0·027)	2 (0·011)	0·26
Altered mental status	0 (0)	2 (0·011)	0·50
Elevated alanine aminotransferase	1 (0·005)	1 (0·005)	0·98
Respiratory distress	1 (0·005)	0 (0)	0·50
Haemorrhage	0 (0)	1 (0·005)	0·50
Complicated abortion	0 (0)	1 (0·005)	0·50
All grade 3–4 adverse events	54 (0·295)	43 (0·227)	0·22
All serious adverse events	12 (0·066)	19 (0·100)	0·26
Grade 3–4 adverse events possibly related to study drugs	1 (0·005)	9 (0·047)	0·040

QTc=corrected QT interval. *Denominators in this section are each dose of study drugs the participants received (ie, women received study drugs repeatedly every 4 weeks during the study). †Number of events (incidence per person-year at risk). ‡Individual adverse events were assessed and graded according to standardised criteria at every visit to the study clinic.[12] §Grade 1–4 adverse events. Includes only those with at least 50 total events.

Table 3: **Safety and tolerability outcomes**

dihydroartemisinin–piperaquine group). Of the ten grade 3–4 adverse events deemed by the investigators to be possibly related to study drugs, nine were QTc prolongation (all in the dihydroartemisinin–piperaquine group) and one was anaemia (in the sulfadoxine–pyrimethamine group).

No maternal deaths occurred during pregnancy; however, four women died during the 6-week postpartum follow-up period (three assigned to dihydroartemisinin–piperaquine and one assigned to sulfadoxine–pyrimethamine). Two women died from post-partum haemorrhage (both in the dihydroartemisinin–piperaquine group), one died of severe pneumonia in the sulfadoxine–pyrimethamine group, and one died of pulmonary tuberculosis in the dihydroartemisinin–piperaquine group. None of these deaths were judged to be related to treatment.

Discussion

In this double-blind, randomised, controlled trial of monthly intermittent preventive therapy, dihydroartemisinin–piperaquine was associated with 96% protective efficacy in reducing in the incidence of symptomatic

malaria, 98% protective efficacy in reducing the prevalence of parasitaemia detected by microscopy, and 50% protective efficacy in reducing the risk of anaemia during pregnancy compared with sulfadoxine–pyrimethamine, the current standard of care. At delivery, dihydroartemisinin–piperaquine was associated with a more than 90% reduction in the detection of malaria parasites and 54% reduction in histopathologically confirmed placental malaria. However, despite notable differences in malaria-specific outcomes, there were no significant differences in the risks of adverse birth outcomes—our primary endpoint—between the two treatment groups.

Despite historical evidence for benefits of intermittent preventive therapy during pregnancy with sulfadoxine–pyrimethamine, there is concern that increased resistance has compromised its effectiveness. In much of eastern and southern Africa, more than 90% of parasites harbour five mutations (three mutations in the dihydrofolate reductase [*dhfr*] gene and two mutations in the dihydropteroate synthase [*dhps*] gene) that have been associated with the failure of sulfadoxine–pyrimethamine to clear existing infections and prevent new infections in pregnant women,[18,19] and additional mutations likely to further compromise the efficacy of intermittent preventive treatment with sulfadoxine–pyrimethamine are now emerging in east Africa.[5] The spread of sulfadoxine–pyrimethamine resistance prompted evaluation of alternative older regimens for intermittent preventive treatment in pregnancy in clinical trials, including mefloquine, amodiaquine alone or combined with sulfadoxine–pyrimethamine, and azithromycin combined with chloroquine or sulfadoxine–pyrimethamine.[20–24] However, these alternative regimens were poorly tolerated or failed to demonstrate clear benefits over sulfadoxine–pyrimethamine.

By contrast with older antimalarial drugs, the ACTs offer an attractive alternative to sulfadoxine–pyrimethamine during pregnancy. In a systematic review comparing sulfadoxine–pyrimethamine with ACTs for treatment or chemoprevention, placenta-positive rates for malaria parasites were unacceptably high in most sulfadoxine–pyrimethamine trial groups, and ACTs provided the lowest parasitological failure rates.[25] Several randomised controlled trials have shown that ACTs are safe and effective for the treatment of malaria during pregnancy.[26–29] Although WHO has endorsed ACTs as first-line treatment for malaria during pregnancy, most infections are asymptomatic and therefore are not treated, stimulating interest in expanding the role of ACTs to intermittent preventive treatment during pregnancy. The most attractive option for this treatment approach is dihydroartemisinin–piperaquine, given its safety, efficacy, and long post-treatment prophylactic effect. So far, two randomised controlled trials have evaluated its use in intermittent preventive treatment in pregnancy. A study from Kenya assessed three regimens: intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine or dihydroartemisinin–piperaquine given at the time of each antenatal visit (median of three doses during pregnancy); and intermittent screening and treatment with dihydroartemisinin–piperaquine, in which women were screened for parasitaemia with a rapid diagnostic test at each antenatal visit, and only given dihydroartemisinin–piperaquine if parasitaemia was detected.[9] Compared with intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine, dihydroartemisinin–piperaquine was associated with significant reductions in the incidence of malaria (84%), parasite prevalence (63%), and parasitaemia at delivery (68%). However, the risks of low birthweight or preterm birth did not differ between these treatment groups. Notably, intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine was associated with a lower risk of perinatal death than was treatment with sulfadoxine–pyrimethamine. The intermittent screening and treatment group was ineffective, as has also been recorded in studies of intermittent screening and treatment with dihydroartemisinin–piperaquine in Malawi[30] and artemether–lumefantrine in west Africa,[31] and WHO recently concluded that intermittent screening and treatment based on available rapid diagnostic tests should not be recommended.[32] In a study conducted by our group in Uganda, women were randomly assigned to intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine or dihydroartemisinin–piperaquine given every 2 months (up to three doses during pregnancy) or dihydroartemisinin–piperaquine given monthly (up to seven doses during pregnancy).[10] Similar to the results of the study in Kenya, both dihydroartemisinin–piperaquine groups were associated with substantial reductions in the incidence of malaria, parasite prevalence, and parasitaemia at delivery compared with the sulfadoxine–pyrimethamine group. Additionally, monthly dihydroartemisinin–piperaquine was associated with a lower incidence of malaria and parasite prevalence than was dihydroartemisinin–piperaquine given every 2 months. Although the results suggested trends towards a reduced risk of low birthweight and preterm birth in the monthly dihydroartemisinin–piperaquine group, these differences were not statistically significant, and there were no differences in the risks of perinatal death between the three groups. Importantly, both the proportion of women enrolled who were primigravid and the risk of low birthweight in the control group were higher in our earlier Ugandan study than in both the Kenya study and the present study. In July, 2015, the WHO Malaria Policy Advisory Committee reviewed findings from the two published studies and concluded that dihydroartemisinin–piperaquine is a promising alternative to sulfadoxine–pyrimethamine for intermittent preventive treatment in pregnancy, but that additional studies are needed to assess differences in adverse birth outcomes and collect additional data for the safety of administering repeated doses of dihydroartemisinin–piperaquine (with particular attention to QTc prolongation).[32] The WHO also

recommended that comparisons should be with monthly sulfadoxine–pyrimethamine, in line with updated recommendations for the timing of intermittent preventive treatment in pregnancy.

In this trial, we aimed to address some of the limitations of previous studies by dosing both intermittent preventive treatments in pregnancy groups once per month; powering the study to detect a difference in a composite adverse birth outcome; and collecting additional safety data, including ECG measurements, in all women at multiple timepoints during pregnancy. In this study, protective efficacies were higher than 90% against most malaria-specific outcomes and 50% against maternal anaemia during pregnancy, consistent with the monthly dihydroartemisinin–piperaquine group in the previous study from Uganda. By contrast, less frequent dosing of dihydroartemisinin–piperaquine in the previous studies from Uganda and Kenya was associated with lower protective efficacies against malaria-specific outcomes and no significant protection against maternal anaemia during pregnancy.[9,10] Although caution is needed when comparing results across different studies, these findings provide further support for dosing dihydroartemisinin–piperaquine once a month during pregnancy and clear evidence that this treatment regimen is superior to sulfadoxine–pyrimethamine for the prevention of malaria in areas with high levels of sulfadoxine–pyrimethamine resistance. Surprisingly, the substantial reductions in the burden of malaria during pregnancy seen with monthly dihydroartemisinin–piperaquine in this study and others has not translated into significant reductions in risks of adverse birth outcomes including low birthweight, preterm birth, and small for gestational age. There are several possible explanations for this apparent paradox. First, individual trials might have been underpowered to detect statistically significant, but clinically important, differences in adverse birth outcomes. Indeed, although a composite adverse birth outcome was used as the primary endpoint for this study, estimates used for sample size calculations were lower than what were actually observed for the risk of the outcome in the control group (30% *vs* 18%), the effect size (30% *vs* 12%) and the proportion of women enrolled who completed follow-up (95% *vs* 85%). Indeed, given what was actually observed, the study had only 12% power to detect a significant difference in the primary outcome between the two treatment groups. Second, the attributable risk of malaria in pregnancy on adverse birth outcomes and thus the potential benefit of effective intermittent preventive treatment in pregnancy might be quite low or modified by other factors such as gravidity. Indeed, several studies, including this one, have found that associations between malaria in pregnancy and low birthweight and associations between intermittent preventive treatment in pregnancy and low birthweight were stronger in primigravid than in multigravid women.[33] Last, sulfadoxine–pyrimethamine might potentially improve birth outcomes independent of its antimalarial activity. Unlike dihydroartemisinin–piperaquine, sulfadoxine–pyrimethamine has broad-spectrum antimicrobial activity, and increasing the number of doses of sulfadoxine–pyrimethamine has been associated with increased protection against sexually transmitted and reproductive tract infections, and with decreased adverse birth outcomes in settings with low levels of malaria transmission.[34,35] A broader issue is what criteria should be used when making policy decisions regarding the optimal regimen for intermittent preventive treatment in pregnancy. Historically, policy recommendations for intermittent preventive treatment in pregnancy have been mainly driven by differences seen in adverse birth outcomes (or, more specifically, low birthweight) from controlled trials. However, non-malarial causes of adverse birth outcomes are multifactorial and often unmeasured. The inability to control for potential unmeasured confounders and estimate the attributable risk of malaria in pregnancy on adverse birth outcomes is a limitation of most clinical trials of intermittent preventive treatment in pregnancy, including this study. Indeed, the true effect size of intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine compared with sulfadoxine–pyrimethamine on adverse birth outcomes might be quite small, and therefore studies with very large numbers of participants are needed.

Tolerability and safety are important considerations when evaluating drugs for routine use during pregnancy. In this study, both drug regimens were well tolerated, with no clinically important differences in the risks of adverse events, consistent with previous studies.[9,10] Of particular interest in this study was the potential for cardiotoxicity with repeated dosing of dihydroartemisinin–piperaquine. Quinoline antimalarials and structurally related compounds, including halofantrine, quinidine, quinine, chloroquine, amodiaquine, and piperaquine, have long been associated with QTc prolongation.[36,37] Mild QT prolongation is clinically silent but severe prolongation can cause arrhythmias, including torsades de pointes. The clinical relevance of QTc prolongation with dihydroartemisinin–piperaquine has been of concern, although the pro-arrhythmic potential of piperaquine in vitro seems to be lower than that of chloroquine and similar to that of artemether–lumefantrine.[38] In a recent meta-analysis[39] of nearly 200 000 individuals who had received dihydroartemisinin–piperaquine, including 15 188 who received repeated courses, there was only one potentially drug-related sudden unexplained death; the authors concluded that the risk of sudden cardiac death following dihydroartemisinin–piperaquine was not higher than the baseline rate of sudden cardiac death. In another meta-analysis of repeated dosing of dihydroartemisinin–piperaquine,[40] no cardiac events were reported in 3935 recipients involving 18 297 courses of dihydroartemisinin–piperaquine ranging from two to 18 courses per individual. However, this meta-analysis had limited ability

to assess the effect of dihydroartemisinin–piperaquine on QTc prolongation because it only included 56 participants (30 pregnant women) in whom ECGs were done. Our study provides novel findings on associations between repeated dosing of dihydroartemisinin–piperaquine and QTc prolongation in a large number of pregnant women. Dihydroartemisinin–piperaquine was associated with significant QTc prolongation that decreased from an average of 18 ms at 20 weeks gestation to 10 ms at 36 weeks gestation. However, no arrhythmias or clinically significant cardiac adverse events were detected. The findings are consistent with a recent unofficial document from the WHO which concluded that dihydroartemisinin–piperaquine has a low risk of cardiotoxicity that is similar to that of other antimalarial drugs including quinine, chloroquine, and amodiaquine.[36] The only other significant difference in adverse events between the treatment groups in this study was a higher number of congenital anomalies, mostly polydactyly, in the dihydroartemisinin–piperaquine group. This finding is probably spurious, since polydactyly is a common congenital anomaly and has not been previously associated with in-utero dihydroartemisinin–piperaquine exposure. However, the prevalence of adverse events should continue to be monitored in future studies.

This study has some limitations. It was done in an area with high malaria transmission intensity, where 50% of women were smear positive for malaria parasites at enrolment, and therefore the findings might not be generalisable to areas with lower transmission intensity. Women received their first dose of intermittent preventive treatment at 16 or 20 weeks gestational age, which is probably earlier than when most women in sub-Saharan Africa first present for antenatal care. 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 dihydroartemisinin–piperaquine group (since sulfadoxine–pyrimethamine is a single daily dose which was always given directly observed in the clinic, whereas dihydroartemisinin–piperaquine is given once a day for 3 days and only the first daily dose was given directly observed in the clinic). However, this was unlikely to have been a significant factor, since compliance to study drugs administered at home was reported to be higher than 98%. Finally, this study did not evaluate for non-malarial causes of adverse birth outcomes, which could have been differentially affected by the intermittent preventive treatment given.

In summary, in our high malaria transmission setting with widespread antifolate resistance, monthly intermittent preventive treatment in pregnancy with dihydroartemisinin–piperaquine was safe, well tolerated, and associated with a notable reduction in the burden of malaria and maternal anaemia during pregnancy compared with sulfadoxine–pyrimethamine, the current standard of care. However, this antimalarial activity did not translate into significant improvements in birth outcomes, which has historically been the primary efficacy measure for driving policy decisions. These findings add to a growing body of literature indicating that dihydroartemisinin–piperaquine is much more effective than sulfadoxine–pyrimethamine at reducing the burden of malaria in pregnancy in areas with a high level of sulfadoxine–pyrimethamine resistance. Furthermore, policy makers should consider placing a greater emphasis on malaria-specific outcomes when evaluating alternative intermittent preventive treatment in pregnancy regimens. Future research should include pooled analyses of existing studies to improve the precision of estimates of protective efficacy against adverse birth outcomes, evaluations of cost-effectiveness, feasibility studies to assess compliance and effectiveness in real-world settings, and additional clinical trials in other epidemiological settings. Future studies should also consider stratification based on gravidity and combining the potent antimalarial properties of dihydroartemisinin–piperaquine with other drugs, such as sulfadoxine–pyrimethamine or azithromycin, which might offer additional benefits beyond their antimalarial properties, such as the prevention of sexually transmitted diseases and reproductive tract infections which are known to cause adverse birth outcomes.

Contributors

DVH, MRK, and GD conceived the study with input from AK, PJ, MN, and TDC. RK, TO, AK, TDC, and GD developed the procedures and wrote the protocol. RK and TO coordinated the fieldwork with input from AK, MN, and TR. PJ, HO, JA, and PN coordinated the laboratory work. BO provided supervision of the study pharmacy. All authors reviewed the protocol and gave permission for publication.

Declaration of interests

We declare no competing interests.

Data sharing

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 enrolment data, individual participant data, repeated measures during pregnancy, QTc repeated measures, 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/Study/20027) 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.

Acknowledgments

This study was supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (P01 HD059454) and the Bill & Melinda Gates Foundation. We thank the women who participated in the study, the dedicated study staff, practitioners at Masafu General Hospital, and members of the Infectious Diseases Research Collaboration (IDRC).

References

1 Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. *PLoS Med* 2010; **7:** e1000221.

2 Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007; **7:** 93–104.

3 Guyatt HL, Snow RW. Malaria in pregnancy as an indirect cause of infant mortality in sub-Saharan Africa. *Trans R Soc Trop Med Hyg* 2001; **95:** 569–76.

4 Walker PG, ter Kuile FO, Garske T, Menendez C, Ghani AC. Estimated risk of placental infection and low birthweight attributable to *Plasmodium falciparum* malaria in Africa in 2010: a modelling study. *Lancet Glob Health* 2014; **2:** e460–67.

5 Gutman J, Kalilani L, Taylor S, et al. The A581G mutation in the gene encoding *Plasmodium falciparum* dihydropteroate synthetase reduces the effectiveness of sulfadoxine–pyrimethamine preventive therapy in Malawian pregnant women. *J Infect Dis* 2015; **211:** 1997–2005.

6 Ranson H, N'Guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? *Trends Parasitol* 2011; **27:** 91–98.

7 Four Artemisinin-Based Combinations (4ABC) Study Group. A head-to-head comparison of four artemisinin-based combinations for treating uncomplicated malaria in African children: a randomized trial. *PLoS Med* 2011; **8:** e1001119.

8 White NJ. Intermittent presumptive treatment for malaria. *PLoS Med* 2005; **2:** e3.

9 Desai M, Gutman J, L'Lanziva A, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin–piperaquine versus intermittent preventive treatment with sulfadoxine–pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. *Lancet* 2015; **386:** 2507–19.

10 Kakuru A, Jagannathan P, Muhindo MK, et al. Dihydroartemisinin–piperaquine for the prevention of malaria in pregnancy. *N Engl J Med* 2016; **374:** 928–39.

11 WHO Malaria Policy Advisory Committee and Secretariat. Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of eighth biannual meeting (September 2015). *Malar J* 2016; **15:** 117.

12 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS, 2014. http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf (accessed July 5, 2016).

13 Hofmann N, Mwingira F, Shekalaghe S, Robinson LJ, Mueller I, Felger I. Ultra-sensitive detection of *Plasmodium falciparum* by amplification of multi-copy subtelomeric targets. *PLoS Med* 2015; **12:** e1001788.

14 Hopkins H, Gonzalez IJ, Polley SD, et al. Highly sensitive detection of malaria parasitemia in a malaria-endemic setting: performance of a new loop-mediated isothermal amplification kit in a remote clinic in Uganda. *J Infect Dis* 2013; **208:** 645–52.

15 Natureeba P, Ades V, Luwedde F, et al. Lopinavir/ritonavir-based antiretroviral treatment (ART) versus efavirenz-based ART for the prevention of malaria among HIV-infected pregnant women. *J Infect Dis* 2014; **210:** 1938–45.

16 Schmiegelow C, Scheike T, Oesterholt M, et al. Development of a fetal weight chart using serial trans-abdominal ultrasound in an East African population: a longitudinal observational study. *PLoS One* 2012; **7:** e44773.

17 Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014; **384:** 857–68.

18 Desai M, Gutman J, Taylor SM, et al. Impact of sulfadoxine–pyrimethamine resistance on effectiveness of intermittent preventive therapy for malaria in pregnancy at clearing infections and preventing low birth weight. *Clin Infect Dis* 2016; **62:** 323–33.

19 Okell LC, Griffin JT, Roper C. Mapping sulphadoxine–pyrimethamine-resistant Plasmodium falciparum malaria in infected humans and in parasite populations in Africa. *Sci Rep* 2017; **7:** 7389.

20 Clerk CA, Bruce J, Affipunguh PK, et al. A randomized, controlled trial of intermittent preventive treatment with sulfadoxine–pyrimethamine, amodiaquine, or the combination in pregnant women in Ghana. *J Infect Dis* 2008; **198:** 1202–11.

21 Gonzalez R, Mombo-Ngoma G, Ouedraogo S, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. *PLoS Med* 2014; **11:** e1001733.

22 Kimani J, Phiri K, Kamiza S, et al. Efficacy and safety of azithromycin–chloroquine versus sulfadoxine–pyrimethamine for intermittent preventive treatment of *Plasmodium falciparum* malaria infection in pregnant women in Africa: an open-label, randomized trial. *PLoS One* 2016; **11:** e0157045.

23 Luntamo M, Kulmala T, Cheung YB, Maleta K, Ashorn P. The effect of antenatal monthly sulphadoxine–pyrimethamine, alone or with azithromycin, on foetal and neonatal growth faltering in Malawi: a randomised controlled trial. *Trop Med Int Health* 2013; **18:** 386–97.

24 Luntamo M, Kulmala T, Mbewe B, Cheung YB, Maleta K, Ashorn P. Effect of repeated treatment of pregnant women with sulfadoxine–pyrimethamine and azithromycin on preterm delivery in Malawi: a randomized controlled trial. *Am J Trop Med Hyg* 2010; **83:** 1212–20.

25 McGready R, White NJ, Nosten F. Parasitological efficacy of antimalarials in the treatment and prevention of falciparum malaria in pregnancy 1998 to 2009: a systematic review. *BJOG* 2011; **118:** 123–35.

26 PREGACT Study Group, Pekyi D, Ampromfi AA, et al. Four artemisinin-based treatments in African pregnant women with malaria. *N Engl J Med* 2016; **374:** 913–27.

27 Manyando C, Kayentao K, D'Alessandro U, Okafor HU, Juma E, Hamed K. A systematic review of the safety and efficacy of artemether-lumefantrine against uncomplicated *Plasmodium falciparum* malaria during pregnancy. *Malar J* 2012; **11:** 141.

28 McGready R, Tan SO, Ashley EA, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated plasmodium falciparum treatment in pregnancy. *PLoS Med* 2008; **5:** e253.

29 Piola P, Nabasumba C, Turyakira E, et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated *Plasmodium falciparum* malaria: an open-label, randomised, non-inferiority trial. *Lancet Infect Dis* 2010; **10:** 762–69.

30 Madanitsa M, Kalilani L, Mwapasa V, et al. Scheduled intermittent screening with rapid diagnostic tests and treatment with dihydroartemisinin–piperaquine versus intermittent preventive therapy with sulfadoxine–pyrimethamine for malaria in pregnancy in Malawi: an open-label randomized controlled trial. *PLoS Med* 2016; **13:** e1002124.

31 Tagbor H, Cairns M, Bojang K, et al. A non-inferiority, individually randomized trial of intermittent screening and treatment versus intermittent preventive treatment in the control of malaria in pregnancy. *PLoS One* 2015; **10:** e0132247.

32 WHO. Malaria Policy Advisory Committe Meeting: Malaria in pregnancy. Geneva: World Health Organization, 2015.

33 McClure EM, Goldenberg RL, Dent AE, Meshnick SR. A systematic review of the impact of malaria prevention in pregnancy on low birth weight and maternal anemia. *Int J Gynaecol Obstet* 2013; **121:** 103–09.

34 Chico RM, Cano J, Ariti C, et al. Influence of malaria transmission intensity and the 581G mutation on the efficacy of intermittent preventive treatment in pregnancy: systematic review and meta-analysis. *Trop Med Int Health* 2015; **20:** 1621–33.

35 Chico RM, Chaponda EB, Ariti C, Chandramohan D. Sulfadoxine–pyrimethamine exhibits dose-response protection against adverse birth outcomes related to malaria and sexually transmitted and reproductive tract infections. *Clin Infect Dis* 2017; **64:** 1043–51.

36 WHO. Malaria Policy Advisory Committe Meeting: The cardiotoxicity of antimalarials. 2017. http://www.who.int/malaria/mpac/mpac-mar2017-erg-cardiotoxicity-report-session2.pdf (accessed May 5, 2018).

37 White NJ. Cardiotoxicity of antimalarial drugs. *Lancet Infect Dis* 2007; **7:** 549–58.

38 Borsini F, Crumb W, Pace S, et al. In vitro cardiovascular effects of dihydroartemisin-piperaquine combination compared with other antimalarials. *Antimicrob Agents Chemother* 2012; **56:** 3261–70.

39 Chan XHS, Win YN, Mawer LJ, Tan JY, Brugada J, White NJ. Risk of sudden unexplained death after use of dihydroartemisinin–piperaquine for malaria: a systematic review and Bayesian meta-analysis. *Lancet Infect Dis* 2018; **18:** 913–23.

40 Gutman J, Kovacs S, Dorsey G, Stergachis A, Ter Kuile FO. Safety, tolerability, and efficacy of repeated doses of dihydroartemisinin–piperaquine for prevention and treatment of malaria: a systematic review and meta-analysis. *Lancet Infect Dis* 2017; **17:** 184–93.