A systematic review and meta-analysis of dihydroartemisinin-piperaquine versus sulphadoxine-pyrimethamine for malaria prevention in pregnancy

Atinuke Olaleye¹,* | Babasola O. Okusanya² | Olabisi Oduwole³ | Ekpereonne Esu⁴ | Martin Meremikwu⁵

¹Maternal–Fetal Medicine Unit, Department of Obstetrics and Gynecology, Benjamin Carson (Sr) School of Medicine, Babcock University, Ilishan-Remo, Nigeria
²Experimental and Maternal Medicine Unit, Department of Obstetrics and Gynecology, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria
³Department of Medical Laboratory Science, Achievers University, Owo, Nigeria
⁴Department of Public Health, Faculty of Allied Medical Sciences, College of Medical Sciences, University of Calabar, Calabar, Nigeria
⁵Department of Pediatrics, College of Medical Sciences, University of Calabar, Calabar, Nigeria

*Correspondence
Atinuke Olaleye, Department of Obstetrics and Gynecology, Benjamin Carson (Sr) School of Medicine, Babcock University, Ilishan-Remo, Ogun State, Nigeria.
Emails: tinukeoolaleye@gmail.com; olaleyea@babcock.edu.ng

Abstract
Background: Intermittent preventive treatment (IPT) with sulphadoxine-pyrimethamine (SP) is recommended for preventing maternal and fetal effects of malaria in pregnancy. Increasing parasite resistance to SP has necessitated the search for an alternative medication.

Objective: To compare dihydroartemisinin-piperaquine (DP) and sulphadoxine-pyrimethamine in preventing malaria during pregnancy.

Search strategy: Databases including CENTRAL, MEDLINE, and ICTRP were searched until August 2018.

Selection criteria: Randomized and quasi-randomized controlled trials that compared DP with SP given to pregnant women to prevent adverse maternal or fetal effects of malaria were included.

Data collection and analysis: Quality of evidence was determined with GRADE criteria. Effectiveness measures were calculated using odds ratios at 95% confidence intervals.

Results: Three randomized controlled trials were included. Compared with IPT-SP, moderate certainty evidence indicated that women who received IPT-DP had significantly lower risks of clinical malaria during pregnancy. High certainty evidence showed intermittent screening and treatment with DP did not reduce placental malaria or maternal parasitemia at delivery. Effect of DP on low birth weight and adverse birth outcomes was minimal.

Conclusions: Moderate certainty evidence suggests that IPT-DP may reduce maternal and placental malaria compared with IPT-SP, and monthly DP is more effective than SP in reducing placental malaria.

PROSPERO ID: CRD42018084651.

KEYWORDS
Artemisinin-based combination therapy; Dihydroartemisinin-piperaquine; Intermittent preventive treatment; Intermittent screening and treatment; Malaria; Pregnancy; Sulphadoxine-pyrimethamine
1 | INTRODUCTION

Malaria in pregnancy is a serious public health issue. Malaria parasitemia occurring in a pregnant woman is associated with the distinctive risk of placental and fetal involvement. In regions of low malaria endemicity, malaria in pregnancy causes febrile illness, spontaneous abortion, and fetal and maternal death. The condition may be asymptomatic with subclinical placental infection in high endemic regions. In Sub-Saharan Africa, an estimated 6 250 000 pregnant women at risk of *Plasmodium falciparum* infection have placental evidence of malaria infection at the time of delivery.1 Without protective measures in pregnancy, malaria infection can result in the delivery of up to 900 000 low birthweight newborns annually in Africa.2

The WHO recommends the use of sulphadoxine-pyrimethamine (SP) for intermittent preventive treatment (IPT) in pregnancy, as it has been reported to reduce malaria infections and improve maternal and neonatal outcomes.3–6 However, there are increasing reports of resistance to SP,7–10 which may erode the gains obtained from the effect of the intervention. These reports have necessitated the evaluation of the evidence from a growing number of studies assessing other combination therapies as potential alternatives to SP as IPT in pregnancy (IPTp) agents.11–13

Artemisinin-based combination therapy (ACT) has been recommended for the treatment of malaria across all ages, including the second and third trimesters of pregnancy.14 The efficacy, safety, and effectiveness of dihydroartemisinin-piperaquine (DP), an ACT, have been assessed in various trials, with reported effectiveness of 98% or higher in the general population, including pregnant women.15–17 Recent reports from some clinical trials in malaria-endemic regions have shown the potential of DP as an IPTp agent. The monthly prophylactic dosage of DP as an IPTp has also been reported to be feasible.18 In addition, the use of DP for intermittent screening and treatment (IST) of malaria during pregnancy has been reported.12,19 Assessing the use of such an ACT as an agent for chemoprevention of malaria in pregnancy is thus essential.

The objective of this systematic review and meta-analysis was to assess the current evidence on feto-maternal outcomes following the use of DP compared with SP for malaria prevention during pregnancy. We used the methodology outlined in the Cochrane Handbook of Systematic reviews20 to conduct this review.

2 | MATERIALS AND METHODS

These databases were searched from inception up to August 21, 2018: Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (PubMed); EMBASE (OVID); and LILACS (BIREME). The WHO International Clinical Trials Registry Platform (ICTRP: http://www.who.int/ictrp/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) were also searched to August 21, 2018, for trials in progress. A combination of keywords and Medical Subject Headings (MeSH terms) were used to identify studies assessing the effect of IPT-DP on predefined health outcomes. For instance, on PubMed the following were used as search terms: “malaria,” “prophylaxis,” “chemoprophylaxis,” “intermittent preventive treatment,” “intermittent screening and treatment,” and “dihydroartemisinin-piperaquine.”

Our search was restricted to randomized and quasi-randomized controlled trials with DP given as the intervention and SP as the control. The Multilateral Initiative on Malaria (MIM) conference abstracts of April 2018 were also searched. Attempts were made to identify all relevant trials without prejudice to language or publication status. The reference lists of retrieved studies were also reviewed for additional relevant studies. The PRISMA guidelines and flow diagram21 were used to report the search and selection of studies.

The outcomes were prespecified and the primary outcomes were clinical malaria episodes during pregnancy (with the presence of asexual parasites and fever), and placental malaria (as defined by authors). Secondary outcomes included mean hemoglobin and maternal anemia (hemoglobin <11 g/dL); maternal peripheral parasitemia (as defined by authors); low birthweight prevalence (<2500 g); and safety (serious adverse events and other adverse events). Published data were included in this systematic review, thus no ethics committee approval was required.

One of the review authors (EE) conducted a literature search using the electronic search methods described. Two review authors (AO and BO) independently screened the titles and abstracts of the literature search for potentially relevant trials and obtained the full reports of these trials. The eligibility criteria were independently applied to the full reports as published in the review protocol using an eligibility form and publications were scrutinized to ensure each trial was included in the review only once. Disagreements were resolved through discussion with another team member (MM). The included studies were listed, as well as the excluded studies and the reasons for their exclusion. The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration ID CRD42018084651.

Two team members (AO and BO) extracted data from eligible studies using a predefined data extraction form, and independently assessed the risk of bias of each trial using Cochrane methods. Six domains of bias were assessed for each included trial: generation of randomization sequence; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other biases (such as early termination of the trial).

Two review authors (EE and AO) evaluated the quality of evidence for each outcome using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.22 Disagreements were resolved through discussions among all review authors. The quality of the evidence was appraised in the results of the systematic review as high, moderate, low, or very low.

Data obtained were entered into RevMan 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). The software was used to combine data using fixed-effect meta-analysis where it was reasonable to assume the studies estimated the same underlying treatment effect, as was for low birthweight prevalence and maternal peripheral malaria at delivery. Where there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between studies, or substantial statistical heterogeneity detected,
random effects meta-analysis was used to produce an overall summary or average treatment effect as seen in the meta-analysis for placental malaria.

Meta-analysis of dichotomous data was conducted, and the results are presented as summary odds ratio (OR) with 95% confidence intervals (CI), while the incidence rates were analyzed with the generic inverse variance method. Statistical heterogeneity in each meta-analysis was assessed using the I-square ($I^2$) statistics. Heterogeneity was regarded as moderate if an $I^2$ was greater than 40%, substantial if $I^2$ was greater than 60%, and considerable if $I^2$ was greater than 80%. When outcome data were presented in a nonuniform format, narrative summary of results was made, and meta-analysis was not done as seen in maternal adverse events.

3 | RESULTS

The search output identified a total of 348 references, of which 17 were duplicate reports. Five other trials were found registered on Clinicaltrials.gov. Of these, one was a duplicate trial report, while three were yet to be completed. Out of the 336 titles remaining following removal of the duplicate reports, 332 titles and abstracts were screened out. The full-text articles of four studies were retrieved for eligibility screening, after which only three studies met the inclusion criteria for this review. A flow diagram showing study selection is given in Figure 1. The characteristics of the included studies are shown in Table 1 (the excluded studies and the reasons for their exclusion are given in Supplementary information Table S1).
TABLE 1  Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Sample size</th>
<th>Population</th>
<th>Setting</th>
<th>Intervention(s)</th>
<th>Comparison(s)</th>
<th>Outcome(s) reported</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desai et al., 2015</td>
<td>RCT</td>
<td>1546</td>
<td>HIV-negative pregnant women; 16–32 wk of pregnancy</td>
<td>Four rural health facilities in Siaya County, western Kenya</td>
<td>IPT-DP IST-DP</td>
<td>IPT-SP</td>
<td>Malaria infection at delivery (composite of peripheral or placental parasitemia); Incidence of malaria infection and clinical malaria during pregnancy; prevalence of adverse newborn morbidity at birth (composite of either preterm delivery, low birthweight, or small for gestational age); anemia during pregnancy or at delivery</td>
<td>Low</td>
</tr>
<tr>
<td>Kakuru et al., 2016</td>
<td>RCT</td>
<td>300</td>
<td>HIV-negative pregnant women; 12–20 wk of pregnancy</td>
<td>Study clinic and Tororo District Hospital, Tororo, Uganda</td>
<td>Three-dose DP Monthly DP</td>
<td>IPT-SP</td>
<td>Prevalence of placental malaria; incidence of symptomatic malaria; prevalence of parasitemia; anemia during pregnancy; parasitemia at delivery (placental, cord, and maternal blood); incidence of adverse birth outcomes (including a composite of spontaneous abortion, stillbirth, low birthweight, preterm delivery, and congenital anomaly)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Madanitsa et al., 2016</td>
<td>RCT</td>
<td>1873</td>
<td>HIV-negative pregnant women; 16–28 wk of pregnancy</td>
<td>Mpemba and Madziabango Health Centers; Chikwawa District Hospital in southern Malawi</td>
<td>IST-SP</td>
<td>IPT-SP</td>
<td>Adverse live birth outcome (composite of small for gestational age, low birthweight, or preterm); plasmodium infection at delivery in peripheral maternal blood or placenta; fetal loss; maternal anemia; clinical malaria; plasmodium infection; mean birth weight; mean gestational age at delivery; congenital plasmodium infection; neonatal and infant clinical malaria; all-cause severe anemia; perinatal and infant mortality by 6–8 wk</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RCT, randomized controlled trial; IPT, intermittent preventive treatment; DP, dihydroartemisinin-piperaquine; IST, intermittent screening and treatment; SP, sulphadoxine-pyrimethamine.
The risk of bias assessment of the included studies is shown in the risk of bias graph (Fig. 2) and the risk of bias summary (Fig. 3). Tables 2–4 present the effects and quality of evidence according to GRADE.

Three randomized controlled trials involving 3719 participants were included.\textsuperscript{12,19,23} The trials commenced in 2011, 2012, and 2014 in Malawi, Kenya, and Uganda, respectively. The included studies involved pregnant women who were given DP (as routine IPT, a three-dose regimen, monthly regimen, or as IST) and compared with those given SP. In two of the studies, drug administration was partly supervised, as only the initial doses of each drug were given as directly observed therapy.\textsuperscript{12,23} Women in all parity groups were recruited in all studies and results were disaggregated for parity (pauci- and multigravid) in two of the trials.\textsuperscript{12,19}

In the three studies, all participants received long-lasting insecticide-treated nets at enrollment. The trials were individually randomized, with multiple intervention arms, and the results presented for each arm. Kakuru et al.\textsuperscript{23} compared IPT-SP with two IPT-DP regimens: a scheduled three-dose DP regimen and a monthly DP regimen. Study participants assigned to the IPT-SP and scheduled three-dose DP groups received the respective interventions at 20, 28, and 36 weeks of pregnancy, while participants in the monthly DP group received the intervention every 4 weeks from 16 or 20 weeks. Madanitsa et al.\textsuperscript{19} compared IPT-SP versus IST-DP, where study participants made scheduled prenatal visits every 4–6 weeks in the second and third trimesters. For the IST-DP group, study participants were screened for malaria using the rapid detection test (RDT) kit at each visit, and treated with DP, if RDT-positive. Desai et al.\textsuperscript{12} compared IPT-SP versus IPT-DP or IST-DP. The study participants were enrolled at 16–32 weeks of pregnancy and received the interventions at intervals of 4–6 weeks. The mean age of the participants in the three studies was 23.4, 22.5, and 22 years, respectively\textsuperscript{12,19,23}; they were predominantly paucigravid (i.e. primigravid and secundigravid).

### 3.1 Comparison 1: Scheduled three-dose IPT-DP versus IPT-SP

The two RCTs\textsuperscript{12,23} compared feto-maternal outcomes following the use of three doses of DP versus SP as intermittent preventive treatment. Regarding the occurrence of clinical malaria during pregnancy (defined as presence of asexual parasites and fever), one study\textsuperscript{23} reported fewer occurrences of symptomatic malaria events per person-year at risk, in the three-dose DP group (11 events vs 32 in the IPT-SP group). The other study\textsuperscript{12} also reported that rates of clinical malaria during pregnancy were lower in the three-dose IPT-DP group (6.1 events vs 37.9 in the IPT-SP group). Hence, moderate certainty evidence indicates that three doses of DP probably results in a large reduction in clinical malaria during pregnancy (OR 0.17; 95% CI, 0.10–0.29; 1171 participants) (Fig. 4).

Moderate certainty evidence suggests that three doses of DP results in little or no difference in placental malaria reduction (OR 0.73; 95% CI, 0.50–1.06; 2 studies, 1231 participants) (Supplementary information Fig. S1).

One study\textsuperscript{12} indicated that three-dose IPT-DP use was associated with statistically significant lower odds of maternal peripheral parasitemia at delivery compared with women receiving IPT-SP. Moderate certainty evidence indicates that a three-dose DP regimen for IPT probably reduces maternal peripheral malaria at delivery (OR 0.27; 95% CI, 0.15–0.47; 2 studies, 1231 participants) (Supplementary information Fig. S2).

Comparing the occurrence of maternal anemia at delivery (hemoglobin <11 g/dL) between women who received three-dose IPT-DP and those who received IPT-SP, moderate certainty evidence indicates that three-dose DP probably reduces maternal anemia (OR 0.72; 95% CI, 0.54–0.95; 1 study, 1031 participants) (Fig. 5). In both studies, the occurrence of anemia during pregnancy was higher in women who received IPT-SP than in those who received IPT-DP.
Low certainty evidence suggests that three-dose DP may result in little or no difference in the prevalence of low birth weight, when compared with IPT-SP (OR 1.20; 95% CI, 0.73–1.97; 2 studies, 1231 participants) (Supplementary information Fig. S3).

Kakuru et al.\textsuperscript{23} reported no significant differences in maternal adverse events among the treatment groups, except for a higher incidence of dysphagia in the monthly DP group than in the three-dose DP group (P=0.02). Desai et al.\textsuperscript{12} reported a higher incidence of maternal adverse events in the IPT-SP group. Low certainty evidence suggests that a three-dose IPT-DP regimen compared with IPT-SP may be associated with fewer maternal serious adverse events (OR 0.42; 95% CI, 0.29–0.62; 2 studies, 1231 participants) (Supplementary information Fig. S4). Kakuru et al.\textsuperscript{23} reported no clinically important differences in the risk of adverse events among the treatment groups. The maternal deaths reported by Desai et al.\textsuperscript{12} were indicated as unrelated to the intervention or to malaria. Follow-up of participants in both trials was until 6–8 weeks after delivery.

With respect to adverse birth outcomes (i.e. small for gestational age, preterm birth, low birth weight, stillbirth, spontaneous abortion, low certainty evidence suggests little or no difference in the incidence of adverse birth outcomes with three-dose DP compared with IPT-SP (OR 0.94; 95% CI, 0.66–1.34; 2 studies, 1231 participants) (Supplementary information Fig. S4).

### 3.2 Comparison 2: Monthly IPT-DP versus IPT-SP

One study\textsuperscript{23} compared maternal and fetal outcomes following monthly DP doses with the usual three doses of IPT-SP. Moderate certainty evidence indicates that monthly DP probably results in a large reduction in clinical malaria during pregnancy (OR 0.01; 95% CI, 0.00–0.19; 1 study, 206 participants) (Fig. 6).

The study also indicated a statistically significant lower odds of placental malaria following delivery in women who received monthly DP compared with women who received IPT-SP. Moderate certainty evidence thus shows that a monthly DP regimen probably results in a reduction in placental malaria infection (OR 0.23; 95% CI, 0.23–0.74; 1 study, 206 participants) (Fig. 7).

Moderate certainty evidence indicates monthly DP probably results in little to no difference in maternal peripheral malaria parasitemia at delivery (OR 0.89; 95% CI, 0.80–1.00; 1 study, 206 participants) (Supplementary information Fig. S5).

Moderate certainty evidence indicates monthly DP probably results in little to no difference in prevalence of low birth weight (OR 0.57; 95% CI, 0.23–1.43; 1 study, 206 participants) (Supplementary information Fig. S6). Moderate certainty evidence shows that a monthly DP regimen probably results in little to no difference in maternal serious adverse events (OR 0.62; 95% CI, 0.19–2.54; 1 study, 206 participants) (Supplementary information Fig. S7). None of the maternal serious adverse events (SAEs) were reported as being possibly related to the study agents.\textsuperscript{23}

Regarding adverse birth outcomes, moderate certainty evidence suggests that monthly DP probably results in a small, possibly unimportant effect on adverse birth outcomes (OR 0.45; 95% CI, 0.19–1.06; 1 study, 206 participants) (Supplementary information Fig. S7).

### 3.3 Comparison 3: IST-DP versus IPT-SP

Two trials compared feto-maternal outcomes following intermittent screening for malaria using rapid diagnostic test (RDT) and treatment if positive, with DP (IST-DP) versus intermittent preventive treatment with SP (IPT-SP).\textsuperscript{12,19} Evidence on the effect of IST-DP on the incidence of clinical malaria during pregnancy was conflicting. There was substantial heterogeneity I\textsuperscript{2}=75% (Supplementary information Fig. S8), which made pooled estimates unnecessary. While Desai et al.\textsuperscript{12} reported in favor of IPT-SP (crude IRR 1.41; 95% CI, 1.00–1.98; P=0.0475), Madanitsa et al.\textsuperscript{23} reported little or no difference in benefit with the use of IST-DP (crude IRR 0.91; 95% CI, 0.70–1.19; P=0.499).

The studies showed statistically significant lower odds of placental malaria in women who received IST-DP compared with those who received IST-SP. High certainty evidence indicates IST with DP does not reduce placental malaria (OR 1.29; 95% CI, 1.10–1.50; 2 studies, 2903 participants) (Fig. 8). High certainty evidence also indicates IST with DP does not reduce maternal peripheral malaria at delivery (OR 1.49; 95% CI, 1.14–1.92; 2 studies, 2903 participants) (Fig. 9).

In addition, moderate certainty evidence on the prevalence of maternal anemia at delivery (hemoglobin <11 g/dL) indicates IST with DP probably makes little to no difference to maternal anemia (OR 0.88;
TABLE 2  GRADE summary of findings: Three-dose dihydroartemisinin-piperaquine vs intermittent preventive treatment with sulphadoxine-pyrimethamine.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence (GRADE)(^b)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical malaria during pregnancy</td>
<td>Risk with sulphadoxine-pyrimethamine 302 per 1000</td>
<td>Risk with dihydroartemisin-piperaquine (3 doses) 68 per 1000 (41 to 111)</td>
<td>OR 0.17 (0.10–0.29)</td>
<td>200 (1 RCT)</td>
<td>MODERATE(^c,d,e,f)</td>
</tr>
<tr>
<td>Placental malaria</td>
<td>335 per 1000</td>
<td>269 per 1000 (201 to 348)</td>
<td>OR 0.73 (0.50–1.06)</td>
<td>1231 (2 RCTs)</td>
<td>MODERATE(^c,d,e)</td>
</tr>
<tr>
<td>Maternal peripheral malaria at delivery</td>
<td>95 per 1000</td>
<td>28 per 1000 (16 to 47)</td>
<td>OR 0.27 (0.15–0.47)</td>
<td>1231 (2 RCTs)</td>
<td>MODERATE(^c,d,e)</td>
</tr>
<tr>
<td>Maternal anemia assessed with hemoglobin concentration</td>
<td>285 per 1000</td>
<td>231 per 1000 (193 to 273)</td>
<td>OR 0.75 (0.60–0.94)</td>
<td>1031 (1 RCT)</td>
<td>MODERATE(^d,e,g)</td>
</tr>
<tr>
<td>Prevalence of low birth weight</td>
<td>52 per 1000</td>
<td>61 per 1000 (38 to 97)</td>
<td>OR 1.20 (0.73–1.97)</td>
<td>1231 (2 RCTs)</td>
<td>LOW(^c,g)</td>
</tr>
<tr>
<td>Maternal serious adverse events (SAEs)</td>
<td>151 per 1000</td>
<td>70 per 1000 (49 to 100)</td>
<td>OR 0.42 (0.29–0.62)</td>
<td>1231 (2 RCTs)</td>
<td>LOW(^c,e,i)</td>
</tr>
<tr>
<td>Adverse birth outcomes assessed with SGA/LBW/preterm birth/fetal loss</td>
<td>118 per 1000</td>
<td>111 per 1000 (81 to 151)</td>
<td>OR 0.94 (0.66–1.34)</td>
<td>1231 (2 RCTs)</td>
<td>LOW(^c,e,i)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

\(^b\)GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*Risk of bias: downgraded by 1. Drug compliance partially assessed directly, as administration was observed for only the first of three doses per course.

\(^c\)No serious risk of bias.

\(^d\)No serious risk of indirectness: the study population, interventions and methods are appropriate for the review question.

\(^e\)No serious risk of imprecision.

\(^f\)Risk of bias: downgraded by 1. Drug compliance for DP partially assessed directly, as administration was observed on only the first of 3 days per course.

\(^g\)Imprecision: downgraded by 1. There is uncertainty about the magnitude of effect of the intervention, as it fails to exclude benefit or harm.

\(^i\)Inconsistency: downgraded by 1. The effect is not consistent across the trials, though statistical heterogeneity is low.

\(^j\)Imprecision: downgraded by 1. One study (Kakuru et al., 2016) showed a small number of events with wide 95% confidence intervals.
TABLE 3  GRADE summary of findings: Monthly dihydroartemisinin-piperaquine vs intermittent preventive treatment with sulphadoxine-pyrimethamine.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects¹ (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence (GRADE)⁵</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with sulphadoxine-pyrimethamine</td>
<td>Risk with dihydroartemisin-piperaquine (monthly dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical malaria during pregnancy</td>
<td>302 per 1000</td>
<td>4 per 1000 (0 to 76)</td>
<td>OR 0.01 (0.00–0.19)</td>
<td>206 (1 RCT)</td>
<td>Dihydroartemisin-piperaquine (monthly dose) probably results in a large reduction in clinical malaria during pregnancy</td>
</tr>
<tr>
<td>Placental malaria</td>
<td>462 per 1000</td>
<td>261 per 1000 (165 to 389)</td>
<td>OR 0.41 (0.23–0.74)</td>
<td>206 (1 RCT)</td>
<td>Dihydroartemisin-piperaquine (monthly dose) probably reduces placental malaria</td>
</tr>
<tr>
<td>Maternal peripheral malaria at delivery</td>
<td>47 per 1000</td>
<td>4 per 1000 (0 to 77)</td>
<td>OR 0.09 (0.01–1.68)</td>
<td>206 (1 RCT)</td>
<td>Dihydroartemisin-piperaquine (monthly dose) probably results in little to no difference in maternal peripheral malaria at delivery</td>
</tr>
<tr>
<td>Maternal anaemia assessed with: Hemoglobin concentration</td>
<td>349 per 1000</td>
<td>238 per 1000 (173 to 311)</td>
<td>OR 0.58 (0.39–0.84)</td>
<td>527 (1 RCT)</td>
<td>Dihydroartemisin-piperaquine (monthly dose) results in reduction in maternal anaemia</td>
</tr>
<tr>
<td>Prevalence of low birth weight</td>
<td>132 per 1000</td>
<td>80 per 1000 (34 to 179)</td>
<td>OR 0.57 (0.23–1.43)</td>
<td>206 (1 RCT)</td>
<td>Dihydroartemisin-piperaquine (monthly dose) likely results in little to no difference in prevalence of low birth weight</td>
</tr>
<tr>
<td>Adverse events - Maternal serious adverse events</td>
<td>57 per 1000</td>
<td>40 per 1000 (11 to 132)</td>
<td>OR 0.69 (0.19–2.54)</td>
<td>206 (1 RCT)</td>
<td>Dihydroartemisin-piperaquine (monthly dose) probably results in little to no difference in adverse events - Maternal serious adverse events</td>
</tr>
<tr>
<td>Adverse events - Adverse birth outcomes</td>
<td>179 per 1000</td>
<td>89 per 1000 (40 to 188)</td>
<td>OR 0.45 (0.19–1.06)</td>
<td>206 (1 RCT)</td>
<td>Dihydroartemisin-piperaquine (monthly dose) results in a small possibly unimportant effect on adverse birth outcomes</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial.

¹The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

²GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

³No serious risk of bias: there was little loss to follow-up, with adequately described random sequence generation and allocation concealment.

⁴No serious risk of indirectness: patients, interventions, methods, and outcome were appropriate for the review question.

⁵Imprecision: downgraded by 1. The results are from one study with a small sample size.

⁶Risk of imprecision: downgraded by 1. There is uncertainty about the magnitude of effect of the intervention.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk with sulphadoxine-pyrimethamine</th>
<th>Risk with dihydroartemisin-piperaquine (intermittent screening and treatment)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical malaria during pregnancy</td>
<td>423 per 1000</td>
<td>457 per 1000 (389 to 525)</td>
<td>OR 1.15 (0.87–1.51)</td>
<td>803 (2 RCTs)</td>
<td>LOW</td>
<td>Dihydroartemisin-piperaquine (intermittent screening and treatment) may result in little to no difference in clinical malaria during pregnancy</td>
</tr>
<tr>
<td>Placental malaria</td>
<td>307 per 1000</td>
<td>363 per 1000 (327 to 399)</td>
<td>OR 1.29 (1.10–1.50)</td>
<td>2903 (2 RCTs)</td>
<td>HIGH</td>
<td>Dihydroartemisin-piperaquine (intermittent screening and treatment) does not reduce placental malaria</td>
</tr>
<tr>
<td>Maternal peripheral malaria at delivery</td>
<td>145 per 1000</td>
<td>190 per 1000 (162 to 222)</td>
<td>OR 1.39 (1.14–1.69)</td>
<td>2903 (2 RCTs)</td>
<td>HIGH</td>
<td>Dihydroartemisin-piperaquine (intermittent screening and treatment) does not reduce maternal peripheral malaria at delivery</td>
</tr>
<tr>
<td>Maternal anemia assessed with hemoglobin concentration</td>
<td>257 per 1000</td>
<td>233 per 1000 (204 to 265)</td>
<td>OR 0.88 (0.74–1.04)</td>
<td>2903 (2 RCTs)</td>
<td>MODERATE</td>
<td>Dihydroartemisin-piperaquine (intermittent screening and treatment) likely results in a small possibly unimportant effect in maternal anemia</td>
</tr>
<tr>
<td>Prevalence of low birth weight</td>
<td>65 per 1000</td>
<td>81 per 1000 (62 to 104)</td>
<td>OR 1.27 (0.96–1.68)</td>
<td>2903 (2 RCTs)</td>
<td>MODERATE</td>
<td>Dihydroartemisin-piperaquine (intermittent screening and treatment) likely does not reduce prevalence of low birth weight</td>
</tr>
<tr>
<td>Maternal serious adverse events</td>
<td>90 per 1000</td>
<td>86 per 1000 (68 to 109)</td>
<td>OR 0.96 (0.74–1.24)</td>
<td>2903 (2 RCTs)</td>
<td>MODERATE</td>
<td>Dihydroartemisin-piperaquine (intermittent screening and treatment) probably reduces maternal serious adverse events slightly</td>
</tr>
<tr>
<td>Adverse birth outcomes</td>
<td>214 per 1000</td>
<td>236 per 1000 (206 to 269)</td>
<td>OR 1.13 (0.95–1.35)</td>
<td>2903 (2 RCTs)</td>
<td>MODERATE</td>
<td>Dihydroartemisin-piperaquine (intermittent screening and treatment) likely does not reduce adverse birth outcomes</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial.

*aThe risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

bGRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*No serious risk of bias: there was little loss to follow-up, with adequately described random sequence generation and allocation concealment.

*Inconsistency: downgraded by 1. There is minimal overlap of confidence intervals, and considerable heterogeneity (I²=86%, P=0.007).

*No serious risk of indirectness: the study population, interventions, and methods were appropriate for the review question.

*Risk of imprecision: downgraded by 1. There is uncertainty about the magnitude of effect, as the intervention either reduces risk of clinical malaria during pregnancy (by 0.13) or increases it (by 0.51).

*No serious risk of inconsistency: no statistically significant heterogeneity.

*No serious risk of imprecision: the number of events were adequate, with a relatively narrow 95% confidence interval around the estimate of effect.

*Risk of imprecision: downgraded by 1. There is uncertainty about the magnitude of effect, as the intervention either reduces risk of anemia (by 0.26) or increases it (by 0.04).

*Risk of bias: downgraded by 1. In one study, more than 10% of the randomized subjects did not contribute to the analysis of low birth weight.

*Risk of imprecision: downgraded by 1. There is uncertainty about the magnitude of effect, as the intervention either reduces risk of maternal serious adverse events (by 0.26) or increases it (by 0.24).

*Risk of bias: downgraded by 1. In one study, more than 10% of the randomized subjects did not contribute to the analysis of neonatal morbidity (composite of small for gestational age, preterm birth, and low birth weight).
Comparing the occurrence of low birth weight between women who received IST-DP and those who received IPT-SP, moderate certainty evidence indicates IST with DP probably makes little to no difference to prevalence of low birth weight (OR 1.27; 95% CI, 0.96–1.68; 2 studies, 2903 participants) (Supplementary information Fig. S9).

Moderate certainty evidence shows that IST with DP compared with IPT-SP probably makes little to no difference to maternal serious adverse events (OR 0.96; 95% CI, 0.74–1.24; 2 studies, 2903 participants) (Supplementary information Fig. S10).

Regarding adverse birth outcomes, moderate certainty evidence suggests that IST with DP compared with IPT-SP probably makes little to no difference to adverse birth outcomes (OR 1.13; 95% CI, 0.95–1.35; 2 studies, 2903 participants) (Supplementary information Fig. S10).

### 4. Discussion

Malaria in pregnancy causes complications in all trimesters of pregnancy. Intermittent preventive treatment with SP is currently used...
in Sub-Saharan Africa as a cost-effective chemopreventive intervention for malaria in pregnancy with beneficial maternal and fetal outcomes. There are few completed randomized trials of ACT regimens, including DP, as a possible alternative drug for malaria prevention in pregnancy, despite reports of increasing IPT-SP resistance. While this systematic review found only two published trials that assessed the use of DP for IPTp in comparison with SP, a search of major clinical trial registers indicates that there are three ongoing trials of ACT regimens for IPTp. Two published trials compared IST using DP (IST-DP) with IPT-SP. An overview of interventions for the prevention of malaria in pregnancy reported three published trials of ACTs involving DP as either IPT or IST, and suggested DP as a potential alternative to IPT-SP.

The three studies included in this review involved a total of 3719 participants. Two of the trials were conducted in East Africa, and one in Southern Africa. One of the three studies included in the analysis was assessed as having “unclear” overall risk of bias. There was unclear risk of bias in the domain of “blinding” (detection bias), with the study contributing data to all the outcomes, except maternal anemia and maternal adverse events in the three-dose DP group.

Moderate to high certainty evidence indicates that compared with IPT-SP, the three-dose and monthly DP regimens appear to result in a significant reduction in clinical malaria during pregnancy. The longer half-life of DP, in addition to the post-treatment prophylaxis provided by ACTs in general, could contribute to this finding. Studies from East and Southern Africa have reported high levels of SP resistance, with prevalence of *P. falciparum* quintuple mutations nearing fixation levels, and some sextuple mutations. Despite the resistance to SP, previous studies have shown that it is effective in reducing the incidence of clinical maternal malaria and placental infection. It is unclear whether the effect size of other outcomes assessed in this review would vary significantly with respect to marked differences in SP resistance.

The effect of DP on reduction of placental malaria infection was significant for monthly DP dosing, however this effect was not replicated in the other DP approaches, i.e. the three-dose regimen and
IST. Moderate certainty evidence suggests that limiting the number of preventive treatments with DP to three scheduled doses throughout a given pregnancy likely results in a small effect in placental malaria reduction while high certainty evidence indicates IST-DP does not reduce placental malaria. The fact that women on monthly DP are likely to receive more doses of the drug from the period of recruitment till delivery, compared with women in other intervention groups, may be responsible for this finding. However, the methods used to detect placental malaria by the included studies comprised methods that reflected both past and present infection. Though an overview of interventions to prevent malaria in pregnancy suggested a lower risk of active placental malaria infections with three or four courses of IPT-DP, this association was not supported with any certainty of evidence.

Low certainty evidence indicated little to no difference in the prevalence of low birth weight when the three-dose DP regimen, and moderate certainty evidence when monthly DP, was compared with SP. IST-DP did not improve birth weight, as indicated by moderate certainty evidence. The effect of DP on adverse birth outcomes (preterm birth, low birth weight, and small for gestational age) was also minimal.

In comparison with IPT-SP, IST-DP made little or no difference to most maternal and fetal outcomes, except that it probably increases the risk of placental malaria compared with IPT-SP.

Overall, moderate certainty evidence shows that IPT-DP is probably more effective than IPT-SP as preventive treatment for malaria in pregnancy; but IST-DP is probably not effective.

This review used a comprehensive search strategy developed by one of the authors and had two team members independently screen identified studies for eligibility. Although the aim was to be comprehensive, some studies might have been missed because time did not permit hand searching of all the grey literature. Two review authors conducted independent data extraction and risk of bias assessment of included studies.

In conclusion, the efficacy of DP as a potential agent for IPT for malaria in pregnancy reported in this review is limited by few studies and moderate certainty of the evidence. Although also limited by few studies, there is moderate to high certainty of evidence that the use of DP for IST of malaria is not superior to IPT-SP. The findings from the studies included in this review indicate that further high-quality research with large numbers of participants, in settings endemic for malaria infection, is needed to provide reliable evidence for policy and practice recommendations.

**AUTHOR CONTRIBUTIONS**

AO wrote the draft of the background and the methods section, while BO and OO reviewed the draft. EE developed the search strategy and conducted the literature search. AO and BO conducted eligibility screening while AO and OO performed the data extraction. AO and EE conducted the data analysis and GRADE assessment. The draft of the review was written by AO while EE, OO, BO, and MM supervised the review process and commented on drafts of the protocol and the review. All review authors subsequently modified the review and agreed to the contents of the final version.

**CONFLICTS OF INTEREST**

The authors have no conflicts of interest to declare.

**REFERENCES**


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Dihydroartemisinin-piperaquine (3 doses) versus sulfadoxine-pyrimethamine. Placental malaria.

Figure S2. Dihydroartemisinin-piperaquine (3 doses) versus sulfadoxine-pyrimethamine. Maternal peripheral parasitemia at delivery.

Figure S3. Dihydroartemisinin-piperaquine (3 doses) versus sulfadoxine-pyrimethamine. Low birth weight prevalence.

Figure S4. Dihydroartemisinin-piperaquine (3 doses) versus sulfadoxine-pyrimethamine. Adverse events (maternal serious adverse events and adverse birth outcomes).

Figure S5. Dihydroartemisinin-piperaquine (monthly) versus sulfadoxine-pyrimethamine. Maternal peripheral parasitemia at delivery.

Figure S6. Dihydroartemisinin-piperaquine (monthly) versus sulfadoxine-pyrimethamine. Low birth weight prevalence.

Figure S7. Dihydroartemisinin-piperaquine (monthly) versus sulfadoxine-pyrimethamine. Adverse events (Maternal serious adverse events and adverse birth outcomes).

Figure S8. Dihydroartemisinin-piperaquine (intermittent screening and treatment) versus sulfadoxine-pyrimethamine (IPT). Clinical malaria during pregnancy.

Figure S9. Dihydroartemisinin-piperaquine (intermittent screening and treatment) versus sulfadoxine-pyrimethamine (IPT). Maternal anemia.

Figure S10. Dihydroartemisinin-piperaquine (intermittent screening and treatment) versus sulfadoxine-pyrimethamine (IPT). (Maternal serious adverse events and adverse birth outcomes).

Table S1. Characteristics of excluded studies.