Dihydroartemisinin-piperaquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of malaria in pregnancy: a systematic review and individual participant data meta-analysis

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Summary

Background High-grade *Plasmodium falciparum* resistance to sulfadoxine-pyrimethamine in east and southern Africa has prompted trials evaluating intermittent preventive treatment in pregnancy (IPTp) with dihydroartemisinin-piperaquine as an alternative to sulfadoxine-pyrimethamine. We aimed to provide an updated and comprehensive review of trials conducted in areas of *high P. falciparum* resistance that compared the efficacy of two types of IPTp regimens on maternal, birth, and infant outcomes.

Methods We conducted two-stage, individual participant data meta-analyses of randomised trials comparing IPTp with dihydroartemisinin-piperaquine to sulfadoxine-pyrimethamine on maternal, birth, and infant outcomes. We searched the WHO International Clinical Trials Registry Platform, ClinicalTrials.Gov, PubMed, and the Malaria in Pregnancy Consortium Library, on July 30, 2020 (updated on September 24, 2024), without restrictions by publication date, peer-review status, or language. Eligible trials enrolled HIV-uninfected pregnant women, followed participants to delivery, included participants with no prior IPTp use during the current pregnancy, and were conducted in areas with high-level parasite resistance to sulfadoxine-pyrimethamine (i.e., PfDHPS 540E ≥ 90% and/or 581G>0%). Only singleton pregnancies were analysed. The primary endpoint was a composite measure of any adverse pregnancy outcome defined as fetal or neonatal loss, small-for-gestational age, low birthweight, or preterm birth. Summary estimates were generated using a random-effects model. Gravidity subgroup analyses were performed. Causal mediation analyses were used to investigate the maternal mechanisms underlying the effect of IPTp regimens on birth outcomes. The meta-analysis is registered in PROSPERO (CRD42020196127).

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Findings Of 85 screened records, six trials (one multi-country trial) from Kenya, Malawi, Uganda and Tanzania contributed data on 6646 pregnancies. Compared to sulfadoxine-pyrimethamine, dihydroarteminsinin-piperaquine was associated with a 69% [95% CI: 45%–82%] lower incidence of clinical malaria during pregnancy, a 62% [37%–77%] lower risk of placental parasitaemia, and a 17% [0%–31%] lower incidence of moderate maternal anaemia. In contrast, sulfadoxine-pyrimethamine was associated with higher mean maternal weight gain (34 g/week [17–51]). There were no statistically significant differences in the composite adverse pregnancy outcome (RR = 1.05 [0.92–1.19]; I^2 = 48%). Individual components of the primary outcome showed no statistically significant differences in the risks of fetal loss (RR = 0.94 [0.61–1.46]), preterm birth (RR = 0.93 [0.76–1.14]), low birthweight (RR = 1.09 [0.83–1.43]), or neonatal loss (RR = 0.73 [0.42–1.26]), though findings may have been underpowered. Small-for-gestational-age risk was 15% (3%–24%) lower in the sulfadoxine-pyrimethamine arm, particularly among multigravidae (a 22% reduction vs 9% in primigravidae). Among multigravidae, infant stunting and underweight by two months was 20% [8%–30%] and 35% [17%–49%] lower in the sulfadoxine-pyrimethamine arm compared to dihydroartemisinin-piperaquine. Compared to dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine was associated with higher mean newborn birthweight (mean difference (MD) = 50 g [95% CI: 13–88]; p = 0.0090, I^2 = 61%) and BWGA z-scores (MD = 0.12 [95% CI: 0.05–0.20]; p = 0.0012, I^2 = 51%), but not gestational age at birth (MD = 0 weeks [95% CI: –0.11 to 0.12]; p = 0.94; I^2 = 42%). Infant wasting by two months was 13% [3%–22%] lower in the sulfadoxine-pyrimethamine arm, regardless of gravidity. Mediation analyses indicated that 15% [0%–19%] of sulfadoxine-pyrimethamine's superior effect on small-for-gestational-age risk was mediated by its greater impact on gestational weight gain.

Interpretation In areas with high *P. falciparum* sulfadoxine-pyrimethamine resistance, dihydroartemisinin-piperaquine offers superior antimalarial efficacy than sulfadoxine-pyrimethamine. However, replacing sulfadoxine-pyrimethamine with dihydroartemisinin-piperaquine alone may not lead to improved maternal and infant health outcomes. Instead, it could result in slightly reduced gestational weight gain and a modest increase in the risk of small-for-gestational age births, and poor infant growth by two months of age. Future research evaluating alternative strategies for IPTp are needed.

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Keywords: Intermittent preventive treatment in pregnancy; Dihydroartemisinin-piperaquine; Sulfadoxine-pyrimethamine; Non-malarial effects; *Plasmodium falciparum*; Antimalarial resistance

Introduction

In sub-Saharan Africa, malaria infection during pregnancy poses substantial risks for both the mother and fetus, including maternal anaemia, miscarriage, stillbirth, preterm birth (PTB), intrauterine growth restriction, low birthweight (LBW), and neonatal mortality.[1] In 2023, nearly 13 million pregnant women in the WHO African region, which accounts for 94% of *Plasmodium falciparum* cases, were exposed to malaria.[2] To prevent malaria during pregnancy, the World Health Organization (WHO) recommends intermittent preventive treatment of malaria in pregnancy (IPTp).[3] This strategy involves administering full treatment courses of a long-acting antimalarial starting in the second trimester of pregnancy up to delivery, with doses given at least one month apart. Currently, 34 African countries have adopted IPTp into their national malaria policy.[2]

Since 1998, sulfadoxine-pyrimethamine has been the only antimalarial recommended for IPTp. Over the past 30 years, its widespread use has led to the emergence of parasite resistance to sulfadoxine-pyrimethamine, particularly in east and southern Africa.[4,5] Concerns over the limited antimalarial efficacy of sulfadoxine-pyrimethamine has prompted research to evaluate alternative IPTp regimens. Of the numerous antimalarial combinations studied, dihydroartemisinin-piperaquine has been the most promising candidate to replace sulfadoxine-pyrimethamine due to its excellent efficacy, long prophylactic period, and safety profile for pregnant women. A 2018 meta-analysis[6] of the first two trials comparing dihydroartemisinin-piperaquine to sulfadoxine-pyrimethamine[7,8] found that dihydroartemisinin-piperaquine was associated with a significantly lower incidence of clinical malaria, placental malaria, maternal anaemia, and fetal loss.[6] However, impacts on LBW, PTB, and small-for-gestational age (SGA) did not statistically significantly differ between regimens. Thus, the WHO recommended further research to determine whether dihydroartemisinin-piperaquine could be a viable replacement for sulfadoxine-pyrimethamine.[9]

Research in context

Evidence before this study

We searched the World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.Gov, PubMed, and the Malaria in Pregnancy Consortium Library for randomised trials comparing intermittent preventive treatment in pregnancy (IPTp) with dihydroartemisinin-piperaquine to sulfadoxine-pyrimethamine, using the search terms: ("intermittent preventive treatment" OR "IPTp") AND (("sulfadoxine-pyrimethamine" OR "sulphadoxine-pyrimethamine") AND ("dihydroartemisinin-piperaquine")). The initial search was conducted on July 30, 2020, and updated on September 24, 2024, without any restrictions on publication date, peer-review status, or language. We found eight studies, of which six were eligible for inclusion in this meta-analysis. Two previous meta-analyses had been conducted: a 2018 review by Desai et al. that included the first two trials, and a subsequent pooled analysis by Roh et al., in 2020 that included the first three trials and focused disentangling the antimalarial and non-malarial effects of sulfadoxine-pyrimethamine versus dihydroartemisinin-piperaquine. These reviews highlighted the superior antimalarial efficacy of dihydroartemisinin-piperaquine compared to sulfadoxine-pyrimethamine, but suggested the potential superior non-malarial benefits of sulfadoxine-pyrimethamine. A recent meta-analysis by Muthoka et al. evaluated the safety of IPTp with dihydroartemisinin-piperaquine in pregnancy. However, an updated meta-analysis comparing the efficacy of all currently completed trials of IPTp with dihydroartemisinin-piperaquine versus sulfadoxine-pyrimethamine has not been conducted.

Added value of this study

This study represents the first and only meta-analysis using individual participant data from all six available trials conducted in areas with high sulfadoxine-pyrimethamine resistance. By pooling data from 6646 pregnancies across multiple African countries, we were able to conduct a more robust and nuanced analysis comparing the efficacy of dihydroartemisinin-piperaquine to sulfadoxine-pyrimethamine for IPTp. Our findings confirm the superior antimalarial efficacy of dihydroartemisinin-piperaquine but also reveal that, compared to dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine is associated with lower risks of adverse birth and infant outcomes, namely, a lower risk of small-for-gestational age and better early infant growth.

Implications of all the available evidence

The findings of our comprehensive analysis caution against switching from sulfadoxine-pyrimethamine to dihydroartemisinin-piperaquine alone for IPTp, even in areas with very high sulfadoxine-pyrimethamine resistance. Switching could reduce gestational weight gain, lower mean newborn birthweights, and increase the risks of SGA and poor early infant growth, particularly among multigravidae. In primigravidae, these birth outcomes did not statistically significantly differ between treatment arms. Thus, further studies harnessing the potential non-malarial benefits of sulfadoxine-pyrimethamine, while effectively preventing malaria are needed. Additionally, more research is needed to better understand the paradoxical relationship between dihydroartemisinin-piperaquine and sulfadoxine-pyrimethamine, including potential mechanisms through which sulfadoxine-pyrimethamine exerts non-malarial benefits on maternal and infant health outcomes, or repeated courses of dihydroartemisinin-piperaquine during pregnancy may have a negative effect on maternal nutritional states and fetal growth. This research is crucial to optimise malaria prevention strategies in pregnancy and improve maternal and neonatal outcomes in malaria-endemic regions.

Since then, several additional trials from Uganda, Kenya, Malawi, Tanzania, and Nigeria have been conducted,[10–13] three of which were conducted in areas with high *P. falciparum* resistance to sulfadoxine-pyrimethamine.[10–12] While results from these trials consistently demonstrated dihydroartemisinin-piperaquine's superior effect on malaria outcomes, findings were mixed regarding its impact on birth outcomes. Moreover, some trials showed that compared to dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine exhibited a greater effect on mean birthweight,[12,14] mean maternal mid-upper arm circumference (MUAC), and gestational weight gain (GWG).[12] However, these outcomes were not consistently reported across trials, highlighting the need for further assessment.

A recent meta-analysis evaluated the safety of IPTp with dihydroartemisinin-piperaquine in pregnancy.[15] The aim of this current meta-analysis was to provide an updated and comprehensive review of trials conducted in areas of high *P. falciparum* resistance that compared the efficacy of IPTp with dihydroartemisinin-piperaquine to sulfadoxine-pyrimethamine on maternal, birth, and infant outcomes.

Methods

Search strategy and selection criteria

The systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (Appendix 1, pp 3–6). We searched the WHO International Clinical Trials Registry Platform, ClinicalTrials.Gov, PubMed, and the Malaria in Pregnancy Consortium Library database for original articles, abstracts, reports, or protocols using the search term: ("intermittent

preventive treatment" OR "IPTp") AND (("sulfadoxine-pyrimethamine" OR "sulphadoxine-pyrimethamine") AND ("dihydroartemisinin-piperaquine")). The search was conducted on July 30, 2020, and updated on September 24, 2024, without restrictions to publication date, peer-review status, or language.

Trials were eligible if they met the following inclusion criteria: randomised HIV-uninfected pregnant women to either IPTp with dihydroartemisinin-piperaquine or sulfadoxine-pyrimethamine; followed participants to delivery to assess malaria and delivery outcomes; enrolled women with no prior use of IPTp during their current pregnancy; and were conducted in sub-Saharan Africa with high-level parasite resistance to sulfadoxine-pyrimethamine (*P. falciparum* dihydropteroate synthase (PfDHPS) 540E mutation prevalence ≥90% and/or 581G mutation >0%). Data on PfDHPS 540E and 581G prevalence were obtained directly from studies or nearby sites. Treatment arms were excluded if dosing schedules differed between arms and/or study drugs were co-administered with another intervention (e.g., azithromycin or metronidazole). Non-singleton pregnancies were excluded from our analyses.

Data extraction and quality assessment

Screening was conducted by two independent reviewers (MER and JG). Any uncertainties or discrepancies were resolved through discussion with a third reviewer (FtOK) or by contacting trial authors. For each eligible trial, chief investigators were invited to collaborate and contribute their individual participant data. Up to three attempts were made to contact authors to participate in the meta-analysis. A description of the available study outcomes from each study is provided in Appendix 2 (pp 7–11). The Cochrane Risk of Bias tool for randomised trials version 2 (RoB2) was used for bias assessment.[16] The meta-analysis is registered in PROSPERO (CRD42020196127).

Study endpoints

Definitions of study endpoints are provided in Appendix 3 (pp 12–14). The primary endpoint was defined as the risk of any adverse pregnancy outcome, a composite outcome of either miscarriage (fetal loss < 28 gestational weeks), stillbirth (fetal loss ≥ 28 gestational weeks), PTB (delivery < 37 gestational weeks), SGA (birthweight < 10th percentile for gestational age using INTERGROWTH-21st standards[17]); LBW (birthweight <2500 g), and neonatal loss (newborn death within the first 28 days of life). PTB, SGA, LBW, and neonatal loss were only assessed among live births. Secondary endpoints included the individual components of the primary outcome; mean birthweight in grams, gestational age at birth in weeks, birthweight-for-gestational age (BWGA) z-scores using INTERGROWTH 21st standards[17]; incidence of clinical malaria during pregnancy; measures of placental malaria; maternal peripheral malaria infection at delivery; measures of maternal anaemia; maternal MUAC at delivery; and GWG per week in grams. Stillbirth was not analysed separately as it was an extremely rare outcome and would have led to unreliable effect estimates with wide confidence intervals. Instead, we included stillbirths within the composite outcome of fetal loss. For safety analyses, we evaluated the number of maternal and infant grade 3+ or serious adverse events (AEs). For studies with infant AE data available, follow-up period was up to the first post-natal visit.

Post-hoc analyses were performed to evaluate differences in term LBW and infant anthropometric measures between arms. Term LBW was defined as a live newborn weighing <2500 g and ≥37 gestational weeks. Infant outcomes included cumulative incidence of stunting, wasting, and underweight measured from birth to approximately two months of life, and mean differences in length-for-age, weight-for-age, and weight-for-length z-scores at approximately two months of life. Z-scores were calculated according to age and sex based on the 2006 WHO Child Growth Standards[18] using the zscorer R package.[19] Stunting, underweight, and wasting were defined as <2 standard deviations below median WHO standards for length-for-age, weight-for-age, and weight-for-length z-scores, respectively.

Statistical analysis

The study employed a two-stage, individual participant data meta-analysis. In the first stage, individual-level data were analysed to generate study-specific estimates. In the second stage, study-specific estimates were pooled to generate summary estimates using restricted maximum likelihood estimation random-effects models. Between-study heterogeneity was assessed using the I^2 statistic. Prediction intervals were reported for each outcome. Meta-analyses were conducted using the meta R package[20]; forest plots were generated using the metafor R package.[21]

Study-specific estimates were computed using unadjusted models, except for maternal weight gain and MUAC outcomes which adjusted for enrolment values. Binary outcomes were modelled using log-binomial regression to estimate risk ratios. Modified Poisson regression with robust standard errors[22] was used if log-binomial models did not converge. Continuous outcomes were modelled using linear regression to compute mean differences. Incidence rate ratios were estimated using Poisson regression with an offset term of the number of days at-risk between study drug initiation to the last day of pregnancy (for maternal outcomes). Pre-specified safety analyses were conducted only among participants who received at least one dose of IPTp drugs. We conducted pre-specified subgroup analyses to assess effect modification by gravidity (primi-versus multi-gravidae). Additional post-hoc subgroup analyses were conducted based on the expected number of IPTp courses (≥5 versus <5) to assess whether earlier IPTp initiation would modify the

intervention effect. The expected number of IPTp courses for each participant was based on their gestational age at enrolment and the trials's IPTp dosing schedule, with additional details of analyses provided in Appendix 8, p 55. p-values for testing subgroup differences ($p_{subgroup}$) were derived from comparing differences in the Q statistic.

Mediation analyses were conducted to examine the extent to which differences in birth outcomes between IPTp regimens were influenced by maternal outcomes that statistically significantly differed between arms. Mediation analyses were carried out following a potential outcomes framework and used targeted minimum loss estimation to estimate natural indirect (mediated) and direct (non-mediated) effects. Separate analyses were conducted for each mediator using the medoutcon R package.[23] Further details of the analytic approach are described in Appendix 4 (pp 15–16). All analyses were conducted using Stata 16.1 (StataCorp, College Station, TX, USA) and R (version 4.3.2; R Project for Statistical Computing; http://www.r-project.org/).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MER and FOtK had full access to the study data; all authors shared the final responsibility for the decision to submit for publication.

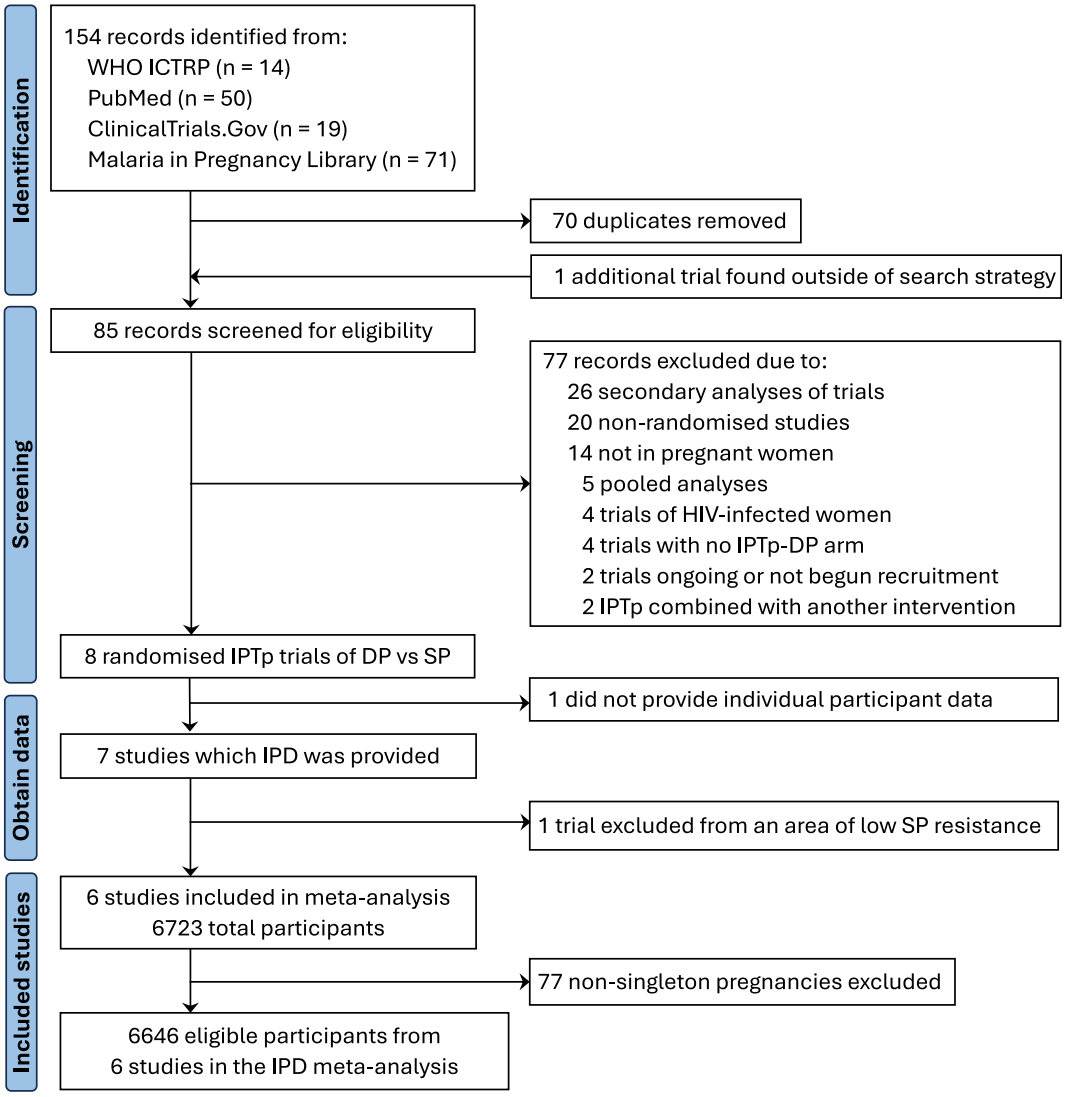

Fig. 1: **PRISMA flow diagram of included studies and participants.** Abbreviations: DP, dihydroartemisinin-piperaquine; IPD, individual participant-level data; IPTp, intermittent preventive treatment of malaria in pregnancy; SP, sulfadoxine-pyrimethamine; WHO ICTRP, World Health Organisation International Clinical Trials Registry Platform.

Results

Our search yielded 154 records (Fig. 1); one additional study (PACTR201701001982152) was found outside the search strategy. After removing duplicates, 85 records were screened, identifying eight randomised controlled trials. All but one study (PACTR201808204807776 from Nigeria) provided individual-level data. This and one additional study from Nigeria (Okoro 2023)[13] were excluded from the meta-analysis due to its location in an area with low sulfadoxine-pyrimethamine resistance;[24] results from the Okoro 2023 trial[13] were presented separately in Appendix 11 (pp 71–75). The remaining six trials (five published[7,8,10–12] and one unpublished[25]) were conducted in Kenya (n = 2), Malawi (n = 2), Uganda (n = 2), and Tanzania (n = 2), where PfDHPS 540E and 581G mutation prevalence ranged from 52% to 99% and 0%–40%, respectively (Appendix 2, p 7). The Madanitsa 2023 trial[12] was conducted in three countries (Kenya, Malawi, and Tanzania); thus, country-specific estimates were reported separately and treated as three distinct studies, bringing the total to eight studies. Individual participant data were obtained from 6723 participants. After excluding 77 non-singleton pregnancies, the final analytic sample comprised 6646 singleton pregnancies. Six of eight studies were scored as having "some concerns" of bias based on their open-label trial design. In addition, two studies did not use ultrasound for gestational age dating (Appendix 5, p 17).

Across studies, enrolment characteristics were balanced between arms (Appendix 6, pp 18–26). LAMP/PCR positivity at enrolment ranged from 11% to 81% across studies. The median number of IPTp courses was 4 [interquartile range (IQR): 3–5] in studies that administered IPTp every four weeks (n = 6 studies[10–12,25]), 2 [IQR: 2–3] in those that administered IPTp every antenatal care visit at 4–6 week intervals depending on gestational age at enrollment (n = 1 study[7]), and 3 [2–3] in those that administered every eight weeks (n = 1 study[8]). In all trials, participants received insecticide-treated nets at enrolment.

Data on the primary endpoint (a composite of any adverse pregnancy outcome) was available from all eight studies (N = 6153 pregnancies). Across studies, the risk of experiencing any adverse pregnancy outcome ranged from 16% to 33% in the sulfadoxine-pyrimethamine arm and 14%–34% in the dihydroartemisinin-piperaquine arm. The pooled RR comparing the risk of any adverse pregnancy outcome between arms was 1.05 [95% CI: 0.92–1.19] (p = 0.51). The I^2 statistic was 48%, indicating moderate between-study heterogeneity. Pooled RRs of the individual components of the primary outcome showed no statistically significant differences in the risks of fetal loss (RR = 0.94 [0.61–1.46]; p = 0.80), PTB (RR = 0.93 [0.76–1.14]; p = 0.47), LBW (RR = 1.09 [0.83–1.43]; p = 0.54), or neonatal loss (RR = 0.73 [0.42–1.26]; p = 0.25), though findings may have been underpowered (Fig. 2A; Appendix 7, pp 28, 30, 33). However, SGA risk was statistically significantly higher in the dihydroartemisinin-piperaquine arm compared to sulfadoxine-pyrimethamine (RR = 1.17 [95% CI: 1.03–1.32]; p = 0.016; I^2 = 3%) (Fig. 2A; Appendix 7, p 29). This effect was mainly seen in multigravidae (RR_{multi} = 1.28 [95% CI: 1.10–1.49] versus RR_{primi} = 1.09 [95% CI: 0.92–1.30]), though testing of subgroup differences did not reach statistical significance ($p_{subgroup}$ = 0.18). The directions for the overall and gravidity subgroup analyses were similar for LBW and term LBW (LBW ≥ 37 gestational weeks), except for the Mlugu 2021 study, where LBW risk was statistically significantly lower in the dihydroartemisinin-piperaquine arm (RR = 0.51 [95% CI: 0.31–0.84]) (Appendix 7, pp 31–32).

Pooled estimates of continuous live birth outcomes showed that compared to dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine was associated with higher mean newborn birthweight (mean difference (MD) = 50 g [95% CI: 13–88]; p = 0.0090, I^2 = 61%) and BWGA z-scores (MD = 0.12 [95% CI: 0.05–0.20]; p = 0.0012, I^2 = 51%), but not gestational age at birth (MD = 0 weeks [95% CI: –0.11 to 0.12]; p = 0.94; I^2 = 42%) (Fig. 2B; Appendix 7, pp 34–36). While study-specific estimates varied for primigravidae, the direction of effect estimates for multigravidae was consistent in all studies except for the Mlugu 2021 study, which found newborn birthweight and gestational age at birth was higher in the dihydroartemisinin-piperaquine arm, regardless of gravidity.

Pooled estimates of malaria endpoints showed that compared to sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine was associated with a 69% [95% CI: 45–82] lower risk of clinical malaria and 61% [95% CI: 45–73] lower risk of maternal peripheral malaria at delivery (Fig. 3; Appendix 7, pp 37 and 42). Regarding placental malaria outcomes assessed by histopathology, dihydroartemisinin-piperaquine was associated with a 31% [95% CI: 18–43] lower risk of past infection and 70% [95% CI: 54–81] lower risk of active infection (Fig. 3; Appendix 7, pp 38 and 41). While substantial heterogeneity was observed between studies (range of I^2 values: 0%–81%), estimates generally favoured dihydroartemisinin-piperaquine for malaria prevention. Subgroup analyses revealed that although the risks of clinical malaria and active placental malaria infection were more than two-fold higher in primigravidae, effect sizes were similar between gravidity subgroups, except for preventing placental pigmentation (past infection only; RR_{primi} = 0.94 [95% CI: 0.83–1.06] versus RR_{multi} = 0.54 [95% CI: 0.39–0.76]; $p_{subgroup}$ = 0.0030) (Appendix 7, pp 38). In addition to its superior effects on malaria prevention, dihydroartemisinin-piperaquine was associated with a lower risk of moderate anaemia (pooled RR = 0.83 [95% CI: 0.69–1.00]; p = 0.050; I^2 = 41%) (Fig. 4A; Appendix 7, p 45).

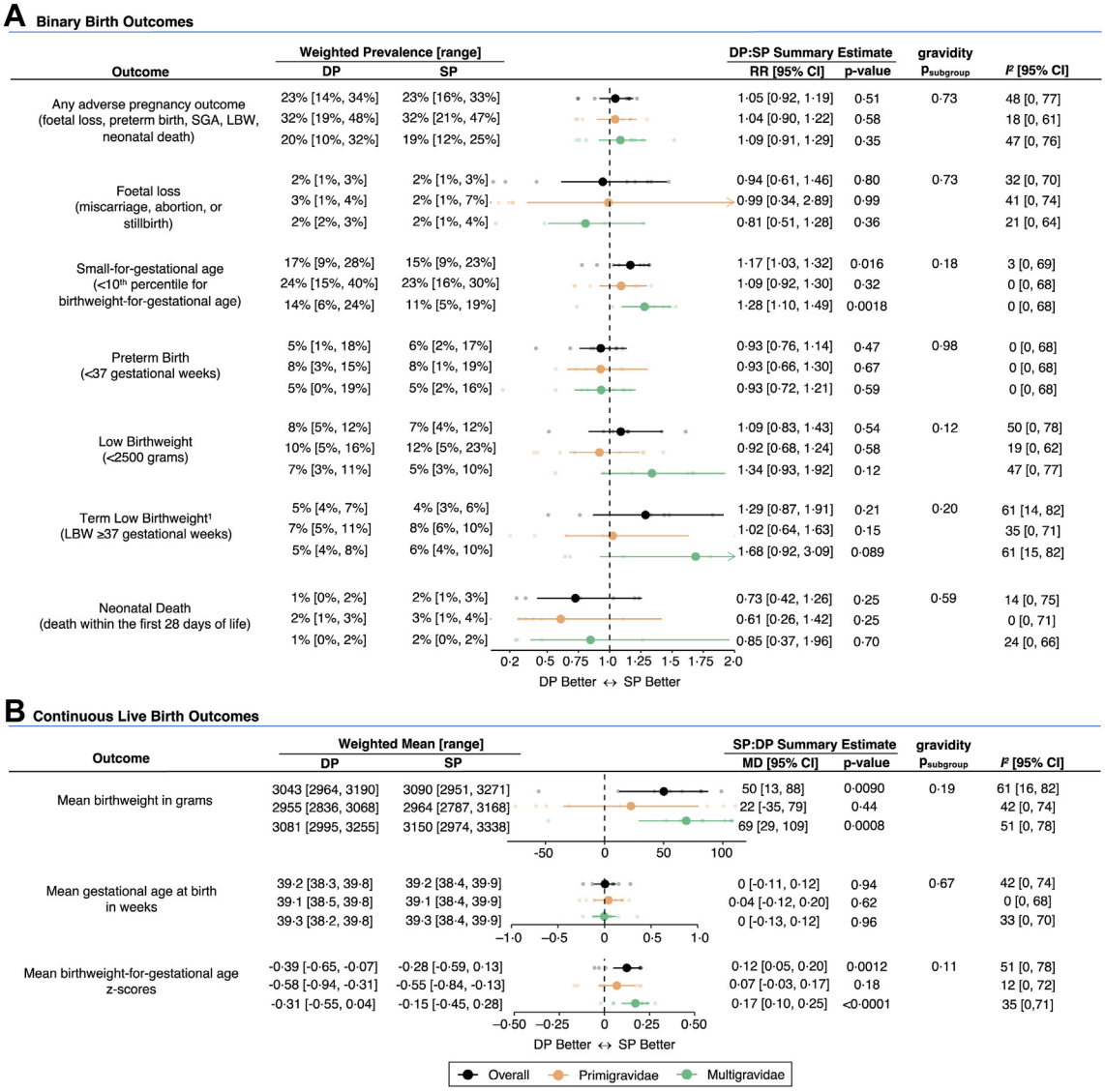

***Fig. 2:* Forest plot comparing binary (A) and continuous live (B) birth outcomes between regimens.** All estimates reflect unadjusted differences between arms. Weighted prevalences and means for each outcome were calculated using a restricted maximum likelihood random-effects model. In the forest plot, dark-shaded circles and error bars represent pooled point estimates and 95% CIs, respectively. Smaller, light-shaded circles indicate study-specific estimates. Gravidity $p_{subgroup}$ represent p-values derived from testing differences between gravidity subgroups using the Q statistic. Abbreviations: CI, confidence interval; DP, dihydroartemisinin-piperaquine; MD, mean difference; RR, relative risk ratio; SP, sulfadoxine-pyrimethamine. [1]Term low birthweight was evaluated in post-hoc analyses and was therefore not included in the composite outcome.

Compared to dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine was associated with higher mean maternal MUAC at delivery (pooled MD = 0.20 cm [95% CI: 0.08–0.32]; p = 0.0011; I^2 = 0%) with the greatest difference in primigravidae (MD_{primi} = 0.40 cm [95% CI: 0.20–0.60] versus MD_{multi} = 0.12 cm [95% CI: –0.02 to 0.27]; $p_{subgroup}$ = 0.030) (Fig. 4B; Appendix 7, p 47). Sulfadoxine-pyrimethamine was also associated with greater GWG (pooled MD = 34 g/week [95% CI: 17–51]; p = 0.0001; I^2 = 42%), with no statistically significant difference by gravidity (MD_{primi} = 47 g/week [95% CI: 18–76] versus MD_{multi} = 27 g/week [95% CI: 6–49]; $p_{subgroup}$ = 0.28) (Fig. 4B; Appendix 7, p 48).

Post-hoc analyses from seven of the eight studies showed that among multigravidae, the risks of stunting and underweight among infants followed from birth up to approximately two months of life were 1.25 [95% CI: 1·09–1·43] and 1.54 [95% CI: 1·20–1·98] times higher in mothers randomised to dihydroartemisinin-piperaquine arm compared to sulfadoxine-pyrimethamine (Fig. 5A;

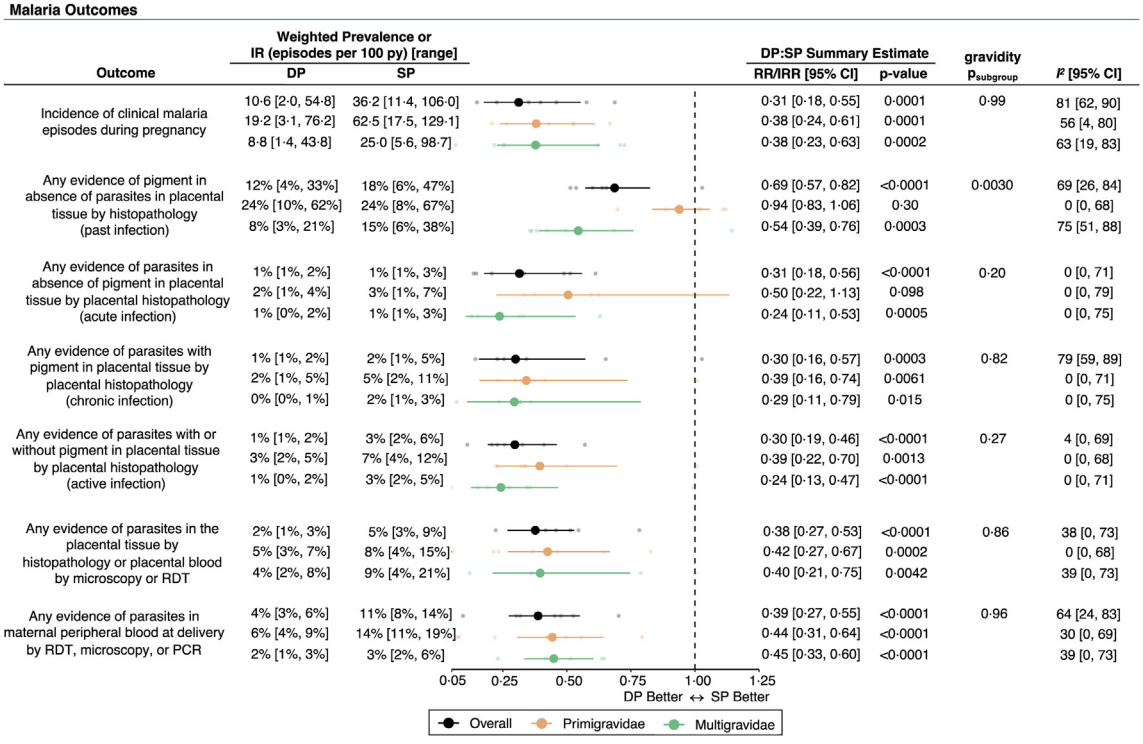

***Fig. 3:* Forest plot comparing malaria outcomes between regimens.** All estimates reflect unadjusted differences between arms. Weighted prevalence and incidence rates for each outcome were calculated using a restricted maximum likelihood random-effects model. In the forest plots, dark-shaded circles and error bars represent pooled point estimates and 95% CIs, respectively. Smaller, light-shaded circles indicate study-specific estimates. Gravidity $p_{subgroup}$ represent p-values derived from testing differences between gravidity subgroups using the Q statistic. Abbreviations: CI, confidence interval; DP, dihydroartemisinin-piperaquine; IR, incidence rate; IRR, incidence rate ratio; PCR, polymerase chain reaction; py, person-year; RDT, rapid diagnostic test; RR, relative risk ratio; SP, sulfadoxine-pyrimethamine.

Appendix 7, pp 49–51). The risk of early wasting was higher in infants born to mothers randomised to dihydroartemisinin-piperaquine arm, regardless of gravidity (RR = 1.15 [95% CI: 1.03–1.29]). Continuous measures of infant growth showed similar results, except mean weight-for-length z-scores, which were higher in the dihydroartemisinin-piperaquine arm, especially among multigravidae (MD_{multi} = 0.13 [95% CI: 0.02–0.25]) (Fig. 5B; Appendix 7, pp 52–54).

Post-hoc subgroup analyses were conducted to explore whether initiating IPTp earlier (and thus expected to receive more IPTp courses) would modify treatment effects (Appendix 8, pp 55–65). Appendix 6 (pp 18–26) provides the expected and actual number of IPTp courses received per arm in each study. We found that the superior effects of sulfadoxine-pyrimethamine on SGA risk was more pronounced among participants expected to receive ≥5 IPTp courses (i.e., those enrolled ≤20 gestational weeks) as compared to those expected to receive fewer IPTp courses (i.e., enrolled >20 gestational weeks) ($RR_{\geq 5\ courses}$ = 1.39 [1.16–1.65] versus $RR_{<5\ courses}$ = 1.03 [0.84–1.27]; $p_{subgroup}$ = 0.033) (Appendix 8, p 57). In contrast, PTB risk was lower in the dihydroartemisinin-piperaquine arm in participants expected to receive ≥5 IPTp courses, a pattern that was less evident among participants expected to receive fewer IPTp courses ($RR_{\geq 5\ courses}$ = 0.75 [0.55–1.02] versus $RR_{<5\ courses}$ = 1.15 [0.87–1.57]; $p_{subgroup}$ = 0.058) (Appendix 8, p 58). We found no statistically significant effect modification of treatment effects by timing of IPTp initiation on composite adverse pregnancy outcome ($p_{subgroup}$ = 0.53), LBW ($p_{subgroup}$ = 0.72), term LBW ($p_{subgroup}$ = 0.82), mean birthweight ($p_{subgroup}$ = 0.71), stunting ($p_{subgroup}$ = 0.75), clinical malaria incidence ($p_{subgroup}$ = 0.44), moderate anaemia ($p_{subgroup}$ = 0.77), or GWG ($p_{subgroup}$ = 0.25), though these analyses may have been underpowered (Appendix 8, pp 56, 59–65).

We conducted mediation analyses to examine the extent to which differences in BWGA z-scores between regimens were mediated by variations in the incidence of clinical malaria, placental malaria (defined as any evidence of parasites or pigment), GWG, and maternal MUAC (Appendix 9, pp 66–69). Pooled estimates showed that dihydroartemisinin-piperaquine's superior effect on preventing placental malaria infection

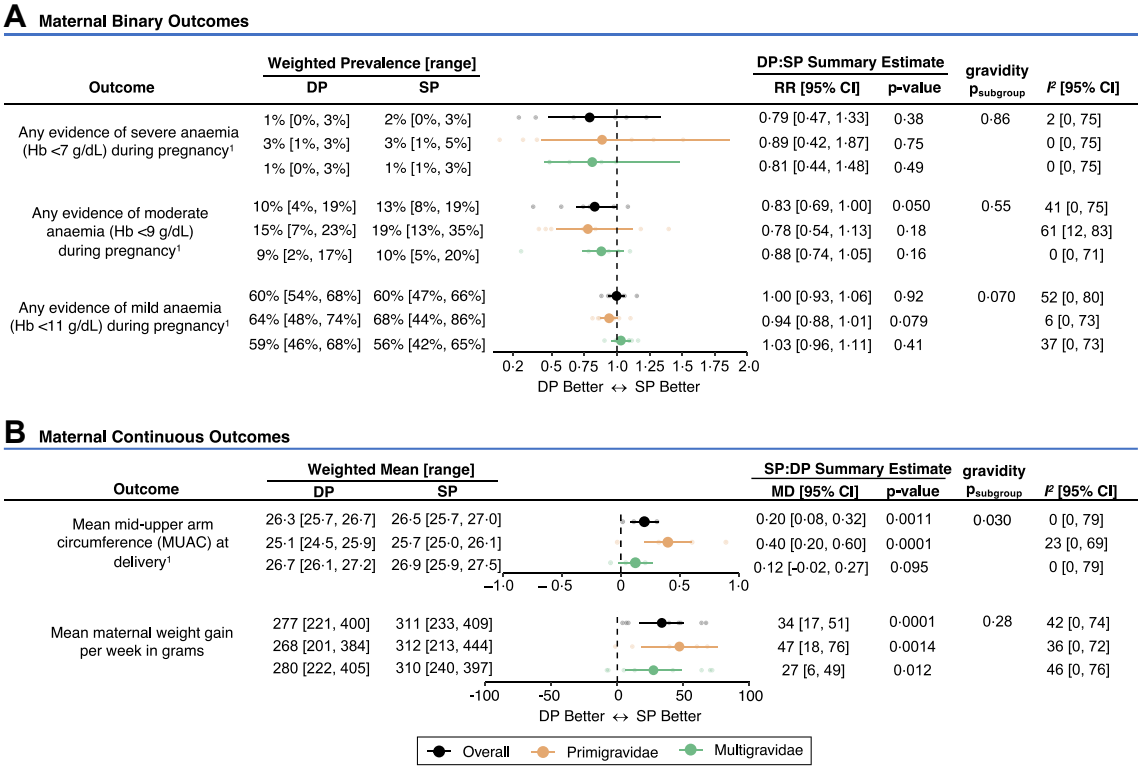

***Fig. 4:* Forest plot comparing binary (A) and continuous (B) maternal outcomes between regimens.** All estimates reflect unadjusted differences between arms, except for mean MUAC and gestational weight gain, which adjusted for enrolment values. Weighted prevalence and means for each outcome were calculated using a restricted maximum likelihood random-effects model. In the forest plot, dark-shaded circles and error bars represent pooled point estimates and 95% CIs, respectively. Smaller, light-shaded circles indicate study-specific estimates. Gravidity $p_{subgroup}$ represent p-values derived from testing differences between gravidity subgroups using the Q statistic. Abbreviations: CI, confidence interval; DP, dihydroartemisinin-piperaquine; Hb, haemoglobin; MD, mean difference; MUAC, mid-upper arm circumference; RR, relative risk ratio; SP, sulfadoxine-pyrimethamine. [1]Maternal anaemia summary derived from seven of eight studies (except the Gutman unpublished study which only had haemoglobin measurements at delivery); Maternal MUAC summary estimates derived from five of eight studies (except the Kakuru 2016; Kajubi 2019; and Mlugu 2021 studies).

contributed a modest proportion to improving BWGA z-scores, especially compared to sulfadoxine's superior 'non-malarial' effect (dihydroartemisinin-piperaquine's indirect, "antimalarial" effect = 0.01 [95% CI: 0–0.02] versus sulfadoxine-pyrimethamine's direct, "non-malarial" effect = 0.15 [95% CI: 0.07–0.23]). Dihydroartemisinin-piperaquine's antimalarial effect was greatest in the Kajubi 2019 study (indirect effect = 0.10 [95% CI: 0.03–0.17]), where malaria burden was exceptionally high (81% of women had detectable parasitaemia by PCR at enrolment) (Appendix 9, p 66). Similar associations were seen when incidence of clinical malaria during pregnancy was used as the mediator (Appendix 9, p 67). Notably, we found that 15% of sulfadoxine-pyrimethamine's superior effects on BWGA z-scores was mediated by its superior effects on GWG (pooled indirect effect = 0.02 [95% CI: 0–0.04] and pooled direct effect = 0.11 [95% CI: 0.05–0.17]) (Appendix 9, p 68). Of the five studies that measured MUAC at delivery, summary estimates showed differences in maternal MUAC mediated a relatively small proportion (2%) of the superior effect of sulfadoxine-pyrimethamine on BWGA z-scores (Appendix 9, p 69).

Lastly, safety analyses showed the incidence of maternal and newborn grade 3+ or serious AEs ranged from 0.07–0.37 events per person-year in the sulfadoxine-pyrimethamine arm and 0–0.34 events per person-year in the dihydroartemisinin-piperaquine arm (Appendix 10, p 70). Of the five studies with infant AE data available, the incidence of infant grade 3+ or serious AEs ranged from 0.05–1.18 events per person-year in the sulfadoxine-pyrimethamine arm and 0.04–0.98 events per person-year in the dihydroartemisinin-piperaquine arm. Compared to sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine was associated with lower maternal and newborn grade 3+ or serious AEs (IRR = 0.90 [95% CI: 0.74–1.09]), although these findings did not reach

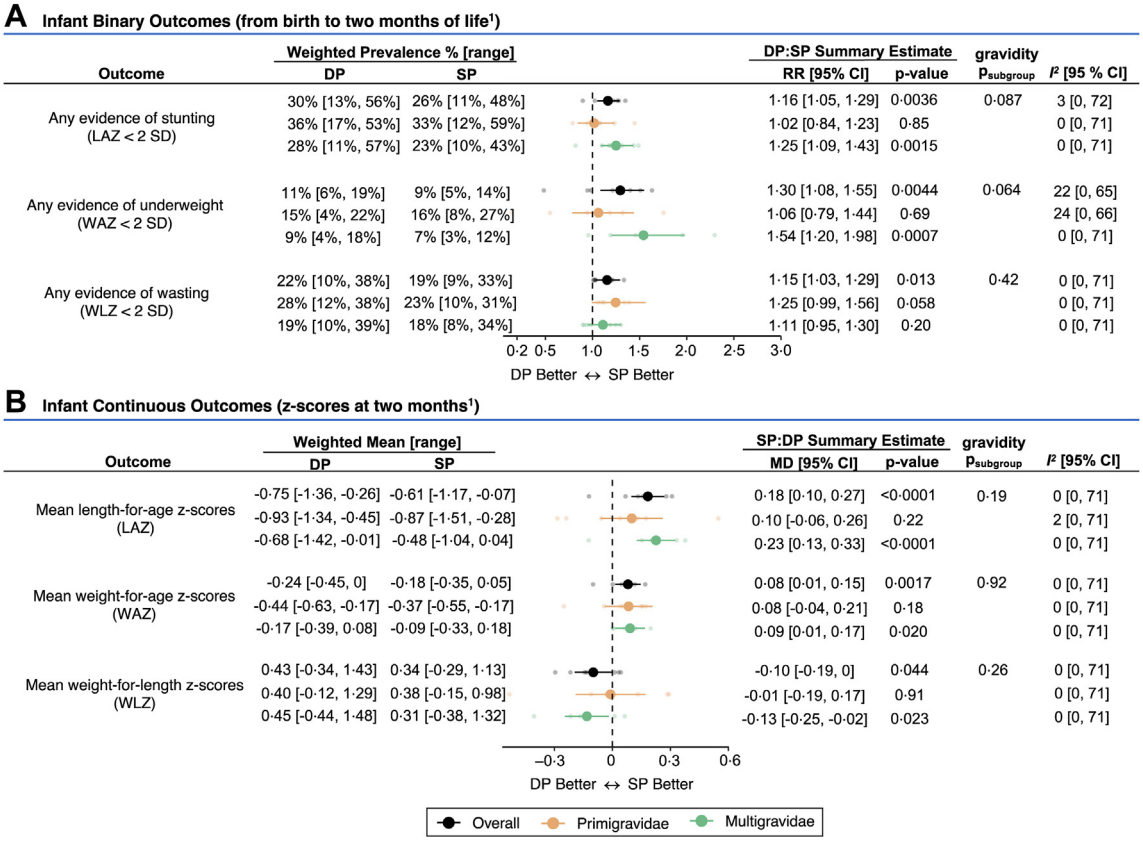

Fig. 5: **Forest plot comparing binary (A) and continuous (B) infant outcomes between regimens.** All estimates reflect unadjusted differences between arms. Weighted prevalence and means for each outcome were calculated using a restricted maximum likelihood random-effects model. In the forest plot, dark-shaded circles and error bars represent pooled point estimates and 95% CIs, respectively. Smaller, light-shaded circles indicate study-specific estimates. Gravidity $p_{subgroup}$ represent p-values derived from testing differences between gravidity subgroups using the Q statistic. Abbreviations: CI, confidence interval; DP, dihydroartemisinin-piperaquine; LAZ, length-for-age z-score; RR, relative risk ratio; SP, sulfadoxine-pyrimethamine; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score. [1]Evaluated in post-hoc analyses; summary estimates derived from seven of eight studies (except the Mlugu 2021 study which did not collect infant follow-up data).

statistical significance (p = 0.27), The incidence of infant grade 3+ or serious AEs was also lower in the dihydroartemisinin-piperaquine arm (IRR = 0.78 [95% CI: 0.61–0.99]; p = 0.044) (Appendix 10, p 70).

Discussion

In this comprehensive meta-analysis, we found that in areas with high *P. falciparum* resistance to sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine was associated with markedly lower risks of clinical, placental, and peripheral malaria infection during pregnancy and did not result in a higher incidence of grade 3+ or serious AEs. However, summary estimates showed that the composite risk of adverse pregnancy outcomes (primary outcome) did not differ between regimens. Analyses of individual components of the composite outcome revealed no statistically significant differences in fetal loss, PTB, or neonatal death, although the study was likely underpowered for these rare outcomes. However, infants of women randomised to sulfadoxine-pyrimethamine had infants with a lower SGA risk and higher mean birthweights, particularly among multigravidae. Results were generally consistent across studies, except for the Mlugu 2021 study, where dihydroartemisinin-piperaquine was associated with a lower risk of LBW and PTB than sulfadoxine-pyrimethamine. Further analyses of maternal outcomes showed that compared to dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine was associated with modestly higher maternal MUAC and GWG, while dihydroartemisinin-piperaquine was associated with a lower risk of moderate anaemia. The differences between treatment arms extended into early infancy whereby infants of women in the sulfadoxine-pyrimethamine arm were less likely to experience stunting, underweight, or wasting in the first two months of life—a critical period with limited

interventions for promoting growth.[26] Collectively, these findings support the continued use of sulfadoxine-pyrimethamine for IPTp but suggest that in areas with high *P. falciparum* sulfadoxine-pyrimethamine resistance, additional interventions are needed to prevent malaria.

Our gravidity subgroup analyses revealed primigravidae and their infants consistently experienced poorer health outcomes than multigravidae. In primigravidae, the comparison of sulfadoxine-pyrimethamine to dihydroartemisinin-piperaquine for SGA risk was closer to the null than in multigravidae. This weaker effect is likely attributable to the stronger impact of dihydroartemisinin-piperaquine on placental malaria, as primigravidae have not yet acquired parity-dependent malarial-immunity.[27] Despite this, we caution against gravidity-dependent approaches to IPTp (i.e., replacing sulfadoxine-pyrimethamine with dihydroartemisinin-piperaquine or adding dihydroartemisinin-piperaquine or another malaria prevention approach to sulfadoxine-pyrimethamine for primigravidae only), as protecting against placental malaria in the first pregnancy could hinder immunity acquisition and increase risks in subsequent pregnancies. Additionally, a gravidity-specific strategy would be logistically more complex to implement.

Our mediation analyses confirm results from prior studies demonstrating sulfadoxine-pyrimethamine's superior impacts on GWG, maternal MUAC, and fetal growth, that has been hypothesised to reflect its 'non-malarial' effect.[12,14,28] Our GWG results support earlier findings from secondary analyses of the Gutman unpublished[28] and Madanitsa 2023 trials.[12] Given its broad-spectrum activity, the precise mechanisms by which sulfadoxine-pyrimethamine enhances fetal and infant growth (either through or independent of GWG) likely involves multiple pathways. Several mechanisms have been proposed including: impacts on enteroaggregative *Escherichia coli*,[28] febrile respiratory illnesses,[29] maternal nutrient absorption in nutritional deficiency-induced enteric dysfunction via a human Intestine Chip model,[30] and maternal inflammation.[26] These non-malarial effects have also been observed in a recent trial comparing monthly sulfadoxine-pyrimethamine with weekly prophylaxis with dihydroartemisinin-piperaquine in children with sickle cell disease. The trial reported less out-patient visits due to non-malaria illnesses, and reduced hospital admissions due to sepsis and acute chest syndrome or pneumonia in the sulfadoxine-pyrimethamine arm.[31] Interestingly, sulfadoxine-pyrimethamine's non-malarial effects were absent in the Kakuru 2016[8] and Mlugu 2021[11] trials, which may suggest that either these mechanisms were less prominent in these trial populations, the antimalarial effects of dihydroartemisinin-piperaquine were greater in these studies, or that dihydroartemisinin-piperaquine could provide comparable non-malarial benefits, although other explanations are possible. Another explanation for the observed differences may include a potential negative effect of dihydroartemisinin-piperaquine on maternal nutritional status and fetal growth, which could accentuate the apparent non-malarial benefits of sulfadoxine-pyrimethamine. It may also be possible that dihydroartemisinin-piperaquine's highly potent antimalarial effect may have prevented pregnancy loss and thus potentially increased the survival of growth-restricted fetuses. However, the low incidence of pregnancy loss (2%) suggests this is unlikely to fully explain the observed differences in SGA risk. Further studies are needed to elucidate the precise mechanisms of both drugs on maternal and fetal growth.

This meta-analysis had several strengths, including comprehensive assessment of maternal, birth, and infant outcomes. However, certain limitations should be considered. First, the small number of included trials restricted our ability to conduct meta-regression analyses, assess for small-study effects, or publication bias. Moreover, the reported I^2 statistics, which can be biased with a small number of studies,[32] should be interpreted cautiously. Second, not all studies included in the meta-analysis were powered for our primary endpoint. Thus, non-statistically significant associations presented in the study should not necessarily be interpreted as absence of effect. Third, mediation analyses were conducted separately for each mediator, limiting our understanding of how these mediators function independently or in combination. Fourth, our mediation estimates may be subject to unmeasured mediator-outcome confounding and measurement error and should be interpreted cautiously. Notably, the absence of data on placental malaria severity, which may be more strongly linked to adverse pregnancy outcomes, could have led to the underestimation of dihydroartemisinin-piperaquine's true antimalarial benefits. Fifth, we assessed infant growth outcomes only up to two months, and additional research is needed to evaluate longer-term effects and other clinically and immunologically important infant outcomes not captured in this study. Sixth, adherence data were not collected. Lastly, in the absence of a no-IPTp control arm, we cannot conclusively state that the observed differences reflect a benefit of sulfadoxine-pyrimethamine or a potential adverse effect of dihydroartemisinin-piperaquine, warranting further investigation.

In conclusion, our meta-analyses showed that, in areas with high *P. falciparum* resistance to sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine was more efficacious in preventing malaria and maternal anaemia. However, if the goal of IPTp is to improve overall maternal, fetal, and infant health outcomes, replacing sulfadoxine-pyrimethamine with dihydroartemisinin-piperaquine alone is unlikely to be more beneficial and could increase the risk of SGA and poor infant growth early in life, particularly for

multigravidae. This may be because sulfadoxine-pyrimethamine offers 'non-malarial' benefits on maternal nutrition and fetal growth. However, a potential negative effect of dihydroartemisinin-piperaquine on maternal nutritional status and fetal growth should be considered. Further research is needed to investigate alternative IPTp regimens and the precise mechanisms of action of both drugs on maternal and fetal growth.

Contributors

MER, JRG, and FOtK conceived the idea for the study. MER, JRG, and FOtK wrote the protocol. JRG, MMa, AK, HCB, SK, JL, FM, RK, MRK, DM, JC, MKL, EM, AARK, EA, OM, RNO, ADG, JDO, JH, MD, PJ, GD, and FOtK collected the original data and provided individual participant data. MER, JRG, and FOtK contributed to data acquisition. MER and JRG conducted the search and identified studies based on the selection criteria; FOtK served as the tiebreaker. MER conducted the bias assessment, with support from FOtK. MER abstracted all the data in collaboration with the investigators of the original trials. MER, JRG, and FOtK accessed and verified the underlying data. MER performed the statistical analysis with inputs from JRG, FOtK, and MMu. MER, JRG, and FOtK wrote the first draft of the manuscript. All authors interpreted the data and critically reviewed the manuscript.

Data sharing statement

Individual participant data from the source trials are available from the investigators from the source trials and will be uploaded onto the Worldwide Antimalarial Resistance Network (WWARN) repository approximately three months after publication.

Declaration of interests

JRG has served as the co-Chair of the Roll Back Malaria, Malaria in Pregnancy Working Group and as a member of the Data Safety Monitoring Boards for the PYRAPREG and ASPIRE trials; no compensation was received. JH and FOtK reports funding from EDCTP2 supported by the European Union (grant number TRIA-2015-1076-IMPROVE), and the MRC/DFID/Wellcome Trust's Joint Global Health Trials scheme, and the Swedish International Development Cooperation Agency. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103202.

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