Dihydroartemisinin-piperaquine versus Sulfadoxine-pyrimethamine for malaria during pregnancy: A systematic review and meta-analysis of randomized controlled trials

Xiajing Chu[1], Meixuan Li[1], Peijing Yan[2], Lufang Feng[1], Jingwen Li[1], Xinrong Liu[1], and Kehu Yang[1]

[1]Lanzhou University
[2]Affiliation not available

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Abstract

Abstract Background Malaria in pregnancy is one of the serious global problems of our time. There were wide concerns about IPT-DP versus IPT-SP for prevention of malaria during pregnancy. Objectives To assess the current latest evidence on the efficacy and safety of dihydroartemisinin-piperaquine versus sulfadoxine-pyrimethamine for malaria in pregnancy. Search Strategy The Cochrane Library, EMBASE, PubMed and Web of science were searched from the earliest publication date available to July 4, 2019 Selection Criteria We included randomized controlled trials comparing dihydroartemisinin-piperaquine with sulfadoxine-pyrimethamine for malaria in pregnancy. Data Collection and Analysis Outcomes were analyzed using Risk ratios (RR) and 95% confidence intervals (CI). We did subgroup analysis about different intervals, including 4-6 or 8 weeks. Main Results A total of five studies with 4660 HIV-uninfected pregnant women in area of high malaria-transmission intensity were included in final synthesis. Meta-analysis showed dihydroartemisinin-piperaquine for intermittent preventive treatment resulted in lower rates of placental malaria (RR=0.50; 95%CI, 0.43–0.59) and infection with malaria parasites at delivery (RR=0.05; 95%CI, 0.01–0.24). In the subgroup analysis, dihydroartemisinin-piperaquine for intermittent preventive treatment at 4-6 weeks of administration was associated with a better effect for infection with malaria parasites at delivery. Conclusions Dihydroartemisinin-piperaquine was a promising alternative drug to sulfadoxine-pyrimethamine for intermittent preventive treatment in settings with high sulfadoxine-pyrimethamine resistance, especially at 4-6 weeks of administration. Based on real-world and other epidemiological settings, more data will be needed to identify the risk of adverse effects.

Tweetable abstract

The efficacy and safety of dihydroartemisinin-piperaquine versus sulfadoxine-pyrimethamine for malaria in pregnancy.

Introduction

Malaria in pregnancy (MIP) is one of the serious global problems and the morbidity was on the rise in some localities[1]. Women are under the higher risk of poor outcomes for malaria transmission during pregnancy[2]. With proper pregnancy-specific protections, most of pregnant women can avoid being infected[3]. The most effective protection was the combination of two antimalarials, which acts at different biochemical sites and increases the useful lifetime of the individual drug[4, 5]. In sub-Saharan Africa, the World Health Organization (WHO) currently recommends intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) for HIV-seronegative pregnant women to reduce malaria[6, 7]. The IPTp-SP means at least twice administration of a single curative dose of SP during pregnancy regardless whether or not the woman is infected[8].

The effectiveness of SP, however, is threatened by increasing resistance in eastern and southern Africa[9, 10]. In fact, resistance is now common against all classes of antimalarial drugs apart from artemisinins[11]. The proposed alternative strategy to IPTp-SP consists of scheduled antenatal testing with rapid diagnostic tests (RDTs) and the treatment of RDT-positive women with artemisinin-based combination therapy (ACT), referred to as intermittent screening and treatment in pregnancy (ISTp). The efficiency and safety of intermittent screening and treatment with dihydroartemisinin-piperaquine (ISTp-DP) had been assessed in many studies[12, 13] and the conclusions remained mixed. Due to the high costs and some side effects, the use of DP in developing countries had been limited[14, 15].

The objective of this systematic review and meta-analysis was to assess the current latest evidence on the efficacy and safety of DP versus SP for malaria in pregnancy. Furthermore, we did subgroup analysis about different intervals, including 4-6 or 8 weeks.

Methods

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) and the Cochrane Collaboration Handbook. At least two reviewers involved in the studies searching, the studies selection, data extraction and assessment of risk of bias. No core outcome sets or patient involvement were used for this meta-analysis.

Eligibility criteria

Trials were considered eligible if they (1) enrolled HIV-seronegative pregnant women; (2)compared DP with SP; (3)provided information on maternal or neonatal outcomes, adverse effects; (4)were a randomized clinical trial conducted;. Studies were excluded if they did not fit the eligibility criteria. Besides, abstracts, reviews and commentaries were excluded (unless they provided additional information from published RCTs).

Information sources

All studies were searched on the Cochrane Library, EMBASE, PubMed and Web of science by two reviewers (Lufang Feng, Xiajing Chu), from the earliest publication date available to July 4, 2019. We also screened the reference lists of relevant reviews and meta-analysis[16].

Search strategy

The search terms included related text words and medical subject headings regarding "DP", "pregnancy" and "malaria". We had tailored search strategy for each database and details of the predefined search criteria were provided in Figure S9 in Supplementary Material.

Study selection

Two independent reviewers (Lufang Feng, Xiajing Chu) removed duplication screened titles, abstracts, full texts by EndNote X9 and agreed on final study eligibility. When disagreements arose, a third investigator (Peijing Yan) was consulted. We recorded the reasons for exclusion of full texts.

Data collection process and data items

Reviewers independently (Xiajing Chu, Jingwen Li) extracted data using a standardized form. The following data was extracted: (1)general information, including first author, country, setting, baseline characteristics of the participants; (2)birth outcomes, including prematurity (<37 GA), low birth weight (a birthweight of a live infant weighing <2,500 g), small for gestational age and overall mortality (stillbirth and spontaneous abortion); (3)maternal outcomes: anemia during pregnancy (haemoglobin <110 g/L), placental malaria by histology and infection with malaria parasites at delivery; (4)adverse effects, such as abdominal pain, cough, diarrhea, chills, headache, malaise.

Risk of bias in individual studies

Two authors (Xiajing Chu, Jingwen Li) independently assessed the risk of bias using the Cochrane Collaboration's tool[17]. When disagreements arose, a third investigator was consulted (Meixuan Li). Each study

was determined as having a low, high, or unclear risk of bias relating to sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Any disagreements were resolved via discussion among the authors[18].

Data analysis

This meta-analysis was performed using Stata, release 14. All results were binary variables and were presented as summary risk ratios (RR) with 95% confidence intervals (CI). We calculated the summary RR and 95% CI by using a fixed effects model. A random effects model was used if the high heterogeneity[19]. The subgroup analysis was conducted according to study type (IST-DP, IPT-DP-4-6w, IPT-DP-8w, IPT-SP-4-6w, IPT-SP-8w).

The influence of study quality on results was assessed by sensitivity analysis. The extent of heterogeneity was interpreted by the total percentage of variation between the studies concerned, measured by theI^2 statistic. The I^2 value was categorized as low if I^2 was 0–25%, moderate if $I^2$was 25–50%, high if I^2 was 50–90%. Additionally, Q-statistic was used to assess the presence of heterogeneity. PQ statistic[?]0.05 was considered to indicate no significant heterogeneity among the included studies[20].

The test of publication bias was not necessary because the included studies were less ten[21].

Results

A total of 10,364 articles were identified initially. After removing 10324 articles, of which 4284 were duplicates, 4191 articles were screened out through title review and 1849 through abstract review, 30 articles were still for further consideration. After excluding 25 studies, the full-text articles of five studies were included in final synthesis (the reasons for their exclusion were given in Figure 1).

Five included RCTs were conducted in 2019, 2018, 2016, 2016, and 2015 respectively and in areas of high malaria-transmission intensity. A total of 4660 HIV-seronegative pregnant were included in this meta-analysis, 2628 in DP groups, 2032 in SP groups (Table 1 presented the characteristics of the included articles). All participants received long-lasting insecticide-treated nets (LLINs) at enrolment. Each dose of DP consists of 40 mg of dihydroartemisinin and 320 mg of piperaquine which was given with a standard 3-d course. SP was composed by 500 mg of sulfadoxine and 25 mg of pyrimethamine per dose. In all five studies, Mwayiwawo Madanitsa[22] compared IPTp-SP with ISTp-DP, where study participants made scheduled antenatal visits every 4–6 weeks (IPT-SP-4-6w). Abel Kakuru, M.D.[14] and Prasanna Jagannathan[23] compared IPTp-SP with two IPTp-DP regimens: one was monthly IPTp-DP regimen (IPT-DP-4w) from 16 or 20 GA, another IPTp-DP group received DP at 20, 28, and 36 GA (IPT-DP-8w). Richard Kajubi[24] compared IPTp-SP with IPTp-DP, every 4 weeks starting at 16 or 20 GA(IPT-DP-4w and IPT-SP-4w). Meghna Desai[13] compared IPTp-SP with IPTp-SP and ISTp-DP. The study participants were enrolled at 16–32 GA and IPTp groups received the interventions at intervals of 4–6 weeks (IPT-DP-4-6w and IPT-SP-4-6w). In subgroup analysis, we treated 4w as 4-6w when comparing IPT-DP with IPT-SP.

Risk of bias based on the Cochrane Collaboration tool were presented in figure 2 and figure 3. All the five studies were randomized controlled trials and had similar group characteristics at baseline[13, 14, 22-24]. Of the five included studies, four had random sequence generation, allocation concealment and selective reporting [13, 22-24]. Two mentioned the blinding of outcome assessment[13, 22] and the blinding of participants and personnel[23, 24]. Only one study had the unclear risk of selective reporting[22]. No studies had incomplete outcome data and other bias.

Birth outcomes

Prematurity

All included trials involving 4845 participants reported the prematurity, with 2363 pregnant women were randomized assigned to receive DP, 2482 were randomized assigned to receive SP [13, 14, 22-24]. The occurrence of prematurity did not differ significantly between the DP and SP groups (RR=1.02; 95%CI, 0.87–1.19; P = 0.83; I2=0.00%; Figure S1; see Supplementary Material). Figure 4-A showed that the occurrence

of prematurity did not differ significantly between the IPT-DP-4-6w and IPT-SP-4-6w, IPT-DP-8w and IPT-SP-8w groups(RR=1.00; 95%CI, 0.70–1.41; P = 0.98; I2=10.20%; Figure 4-A). Figure 4-B showed no significant differences were obtained for prematurity between IST-DP with IPT-SP-4-6w (RR=1.06; 95%CI, 0.89–1.27; P = 0.51; I2=4.50%; Figure 4-B).

Low birth weight

Figure B showed that five articles, with a total of 4644 participants, reported the incidence of low birth weight[13, 14, 22-24]. 2267 randomly assigned to DP group, 2377 randomly assigned to SP group. DP has similar effect compared with SP(RR=1.06; 95%CI, 0.88–1.29; P = 0.524; I2=19.2%; Figure S2). The subgroup analysis indicated similar rates of low birth weight were noted between different intervals of SP and DP(RR=1.00; 95%CI, 0.73–1.38; P = 0.99; I2=0.00%; Figure 5-A). We noted that IST-DP, compared with IPT-SP-4-6w, presented similar rates (RR=1.24; 95%CI, 0.96–1.61; P = 0.10; I2=0.00%; Figure 5-B).

Overall mortality (stillbirth and spontaneous abortion)

Four trials reported the effect of DP and SP on stillbirth (RR=0.66; 95%CI, 0.42–1.05; P = 0.09; I2=33.20%;Figure S3; see Supplementary Material) and three trials reported the incidence of small for gestational age (RR=0.38; 95%CI, 0.03–5.35; P = 0.34; I2=75.60%; FigureS4; see Supplementary Material). The subgroup analysis showed different intervals and regimens of DP were not associated with a better effect of SP (Figure 6-A, Figure 6-B and Figure 7).

Small for gestational age

The incidence of small for gestational age was evaluated in three trials, including 4242 participants, and non-significant reduction was found between DP and SP groups(RR=1.12; 95%CI, 0.91–1.37; P = 0.293; I2=0%; Figure S5; see Supplementary Material). Figure 8 showed IPT-DP-4-6w has similar effects to IPT-SP-4-6w(RR=0.99; 95%CI, 0.72–1.37; P = 0.63; I2=0.00%; Figure 8-A)and IST-DP had similar effects to IPT-SP-4-6w (RR=1.22; 95%CI, 0.96–1.56; P = 0.11; I2=0.00%; Figure 8-B)

Maternal outcomes

Placental malaria by histology

After two histological studies without placental malaria by histology data were excluded, 2255 were randomized to receive DP, 1757 were randomized to receive SP. The fixed effects analysis showed a significant reduction in DP group compared with SP(RR=0.51; 95%CI, 0.44–0.59; P = 0.19; I2=40.30%; Figure S6; see Supplementary Material), a significant 50% reduction in IPT-DP-8w, 54% reduction in IPT-DP-4-6w(RR=0.50; 95%CI, 0.43–0.59; P = 0.00; I2=0.20%; Figure 9).

Infection with malaria parasites at delivery

The incidence of infection with malaria parasites at delivery was assessed in two trials, 585 participants were included, 497 were randomized to receive DP, 1082 were randomized to receive SP. The fixed effects analysis showed a significant reduction in DP groups(RR=0.05; 95%CI, 0.01–0.23; P = 0.00; I2=0.00%; Figure S7; see Supplementary Material). However, this effect was entirely restricted to a significant 99.96% reduction in IPT- DP-4-6w group (RR=0*04; 95%CI, 0.01–0. 27; P = 0.00; I2=0.00%; Figure 10-A), whereas no treatment effect was found in IPT-DP-8w group yet (0*10 [0*01 to 0*71]; Figure 10-B). Therefore, DP is associated with a better effect with 4-6 weeks of administration.

Anaemia during pregnancy (haemoglobin <110 g/L))

Anaemia during pregnancy was performed in two trials. Since the high degree of heterogeneity (I2= 94.7%), a random effects model was used. The random effect model showed non-significant reduction was found between DP and SP groups (RR=0.71; 95%CI, 0.42–1.22; P = 0.22; Figure S8; see Supplementary Material). The subgroup analysis showed similar effects between IPT-DP-4w, IST-DP and IPT-SP-4-6w groups. (RR=1.07; 95%CI, 0.92–1.24; P = 0.36, I2=0.00%; Figure 11-A) (RR=0.96; 95%CI, 0.85–1.08; P = 0.46; I2=0.00%; Figure 11-B).

Adverse effects

Three studies reported the adverse effects which were insufficient with a quantitative analysis[13, 14, 24], one reported 303 maternal and infant serious adverse events[13], which were least frequent in DP group. Only two reported the similar adverse effects[14, 24]. Table 2 presented the characteristics of adverse effects. compared with SP, DP can reduced the risk of abdominal pain, chills, headache, malaise, stillbirth and thrombocytopenia depending on the incidence of per person-year at risk function.

Discussion

Main Findings

To reduce child mortality, WHO reaffirmed reducing the incidence of LBW as an important target of the UN Millennium Development Goal[25]. With the significant augment of malaria parasites at delivery[26], The third edition of Guidelines for the treatment of malaria had strengthened the recommended strength, prompting the use of DP[27].

In this systematic review and meta-analysis of five randomized controlled trials including 4660 HIV-seronegative pregnant women with malaria, we found IPT-DP was a promising alternative option for MIP. All included studies were conducted in high endemic areas[6]. Women who were given IPT-DP-4-6w showed a lower risk of placental malaria and infection with malaria parasites at delivery, without increasing the risk of adverse birth outcomes. DP had the better effectiveness and safety than SP.

Birth outcomes included prematurity, low birth weight, small for gestational age and overall mortality (stillbirth and spontaneous abortion). There was little difference in any interval and regimens of DP and SP. The protection of IPT-SP against adverse birth outcomes has been identified in the cross sectional survey[28] and the prospective cohort study[29]. However, included five trials were conducted in Africa where has high malaria transmission[30]. Women were exposed to antenatal infections more frequently and acquired immunity to prevent adverse outcomes malaria earlier[31]. This may result in the resistance and ineffectiveness of DP and SP[32].

Maternal outcomes such as anemia during pregnancy, placental malaria by histology and infection with malaria parasites at delivery all were direct indicators to reflect the efficacy of antimalarials[33]. In this meta-analysis, IPT-DP may be a better choice to take into account when selecting of first and second line antimalarial. This was consistent with recent research[34]. Few studies had reported the efficacy of IPT-DP-8w, this article suggested that more frequent repetitive doses were needed to improve the efficacy of IPT-DP.

Safety and tolerance are important considerations when determining AEs to malaria routine drugs during pregnancy. Only three studies reported the adverse effects. Through the description of the adverse effects, the IPT-DP-4-6w presented a better effect overall.

Strengths and Limitations

Strengths of this review were:Firstly, this was the recent largest study to compare DP with SP among pregnant women with malaria. We included all available published data and according to accepted guidelines[35]. Besides, this article used a comprehensive search strategy and had two team members independently screen identified studies for eligibility.

The limitations of this study were: Firstly, although the purpose was to be more comprehensive, while due to the lack of search of all the grey literature, some studies might have been missed. Besides, all enrollment women received insecticide-treated bednets[36] and some of them were not paucigravidae[37, 38], these may may lead to the confounding of conclusions. Since the condition of HIV may essentially eliminate the typical pattern of malaria efficacy[39], we only included studies reporting HIV-seronegative pregnant women with malaria. Finally, we just described the proportion of the included adverse effects due to the lack of data.

Interpretation

Although two studies compared DP and SP for MIP[34, 40], the number of participants was small, which might weaken the conclusions and leaded to the low quality of evidence[41]. This study had shown IPT-DP-4w was associated with lower risk of malaria during pregnancy, moderate-to-high grade pigment deposition and improvements in birth outcomes[19]. Therefore, in the subgroup analysis, we divided the IPT-DP into two categories, IPT-DP-4-6w and IPT-DP-8w to get substantially more precise summary results.

Conclusion

Facing the increasing drug pressure, identifying the proper antimalarial in high endemic areas is of critical importance. IPT-DP-4-6w in reducing placental malaria infection and malaria parasite infection during delivery was significant for IPT-SP, but more data were needed to determine the risk of adverse effects with the consideration of real-world and other epidemiological settings.

Disclosure of Interests

The authors declare they have no conflicts of interests. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

Xiajing Chu, Meixuan Li designed and performed the search, selected studies for inclusion, collected data, planned and performed the statistical analyses, Xiajing Chu, Meixuan Li contributed to the interpretation of the results, and drafted the initial and final version of the manuscript. Xiajing Chu, Meixuan Li, and Peijing Yan contributed to the interpretation of the results, and reviewed and revised the manuscript. Xiajing Chu, Meixuan Li, Jingwen Li and Lufang Feng conceptualized and designed the study, contributed to the search, selected studies for inclusion, supervised data collection. Xinrong Liu and Kehu Yang contributed to the statistical analyses and interpretation of the results, and reviewed and revised the manuscript.

Details of ethics approval

Not applicable.

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Table/Figure Caption List

Table 1: The characteristics of the included articles

Table 2: The adverse events in all included studies.

Figure 1: PRISMA flow chart

Figure 2: Risk of bias of overall

Figure 3: Risk of bias in individual studies

Figure 4: Forest plot of prematurity by IPT-DP VS. IPT-SP (Figure4- A) and IST-DP VS. IPT-SP (Figure4-B)

Figure 5: Forest plot low birth weight by IPT-DP VS. IPT-SP (Figure 5-A) and IST-DP VS. IPT-SP (Figure 5-B)

Figure 6: Forest plot of stillbirth by IPT-DP VS. IPT-SP (Figure 6-A) AND IST-DP VS. IPT-SP (Figure6-B)

Figure 7: Forest plot of spontaneous abortion by IPT-DP VS. IPT-SP

Figure 8 Forest plot of small for gestational age by IPT-DP VS. IPT-SP (Figure 8-A) and IST-DP VS. IPT-SP (Figure 8-B)

Figure 9: Forest plot of placental malaria by histology by IPT-DP VS. IPT-SP

Figure 10: Forest plot of infection with malaria parasites at delivery by IPT-DP VS. IPT-SP

Figure 11: Forest plot of anaemia during pregnancy by IPT-DP VS. IPT-SP (Figure11-A) and IST-DP VS IPT-SP (Figure 11-A)

Supplementary data:

Figure S1 Forest plot of prematurity by DP and SP

Figure S2 Forest plot of low birth weight by DP and SP

Figure S3 Forest plot of stillbirth by DP and SP

Figure S4 Forest plot of spontaneous abortion by DP and SP

Figure S5 Forest plot of small for gestational age by DP and SP

Figure S6 Forest plot of placental malaria by histology by DP and SP

Figure S7 Forest plot of infection with malaria parasites at delivery by DP and SP

Figure S8 Forest plot of anaemia during pregnancy by DP and SP

Figure S9 Searching strategy

Table1

	Country	Setting	Comparators (no.)	Maternal ages (year) (mean±sd) ()	Gestational age (week) (mean±sd) ()	Maternal weight (kg) (mean±sd) ()	Maternal weight (kg) (mean±sd) ()	Maternal height (cm) (mean±sd) ()	Maternal height (cm) (mean±sd) ()	Gradivity (no.) (first/Sec third or more)
Richard Kajubi 2019	USA	Uganda	IPT-DP-4w 391 IPT-SP-4w 391	23.0 ± 5.9 23.0 ± 5.9	15.4±0.3 15.0±0.3	15.4±0.3 15.0±0.3	NA NA	NA NA	NA NA	93/105/193 102/85/204
Prasanna Jagannathan 2018	USA	Uganda	IPT-DP-4w 47 IPT-DP-8w 44 IPT-SP-8w 100	23.0 ± 3.8 23.0 ± 4.1 21.4 ± 3.6	NA NA NA	NA NA NA	NA NA NA	NA NA NA	NA NA NA	10/16/21 10/16/18 35/33/32
Mwayiwawo Madanitsa 2016	Malawi	Madziabango Chikwawa	IST-DP 923 IPT-SP-4-6w 921	22.5 ± 5.1 22.6 ± 5.1	16.8±23.3 16.2±23.0	16.8±23.3 16.2±23.0	54.8 ± 7.2 55.4 ± 7.6	54.8 ± 7.2 55.4 ± 7.6	153.8 ± 5.0 154.2 ± 5.0	311/260/35 316/253/35
Abel Kakuru 2016	Uganda	Uganda	IPT-DP-4w 100 IPT-DP-8w 94 IPT-SP-8w 106	22.6 ± 4.0 22.2 ± 4.3 21.3 ± 3.6	15.5±2.1 15.4±2.0 15.2±2.0	15.5±2.1 15.4±2.0 15.2±2.0	55.5±7.5 55.6±7.0 55.4±6.8	55.5±7.5 55.6±7.0 55.4±6.8	162.3 ± 7.7 162.5 ± 6.7 162.8±6.8	36/28/36 33/28/33 42/32/32
Meghna Desai 2015	USA	Bondo Lwak Madiany Siaya	IPT-DP-4-6w 514 IST-DP 515 IPT-SP-4-6w 514	23·4 ± 5·9 23·4 ± 5·5 23·5 ± 6·0	23·0±4·0 22·9±4·7 22·8±4·4	23·0±4·0 22·9±4·7 22·8±4·4	61.8 ± 9.3 61.1 ± 8.3 61.5 ± 9.1	61.8 ± 9.3 61.1 ± 8.3 61.5 ± 9.1	164.3 ± 6.7 164.1 ± 6.8 164.3 ± 6.9	NA NA NA

(RCT=randomized controlled trials, SP=sulphadoxine-pyrimethamine, DP= dihydroartemisinin-piperaquine, IPT=intermittent preventive treatment, IST= intermittent screening treatment, 4w= doses are given every four weeks, 8w= doses are given every eight weeks, 4-6w= doses are given every four-six weeks, = prematurity, = low birth weight, = stillbirth, = spontaneous abortion, = small for gestational age, = placental malaria by histology, = infection with malaria parasites at delivery, = anaemia during pregnancy, = adverse effects)

Table2

Adverse effects	Abel Kakuru,2016*	Abel Kakuru,2016*	Abel Kakuru,2016*	Richard Kajubi,2019*
	IPT-DP-4w	IPT-DP-8w	IPT-SP-8w	IPT-DP-4w
Abdominal pain	2.47	2.52	3.14	4.22
Cough	1.44	1.47	1.72	3.59
Diarrhea	0.24	0.21	0.22	0.35
Chills	0.22	0.29	0.38	0.14
Headache	1.46	1.45	1.64	3.19
Malaise	0.15	0.19	0.29	0.27
Vomiting	0.15	0.17	0.15	0.24
Anemia	0.11	0.08	0.22	0.04
Congenital anomaly	0.00	0.08	0.04	0.05
Stillbirth	0.02	0.02	0.02	0.01
Thrombocytopenia	0.00	0.00	0.04	0.02

*incidence per person-year at risk

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`Figures.docx` available at https://authorea.com/users/304959/articles/435526-dihydroartemisinin-piperaquine-versus-sulfadoxine-pyrimethamine-for-malaria-during-pregnancy-a-systematic-review-and-meta-analysis-of-randomized-controlled-trials