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*Review Article*

# Effects of Intermittent Preventive Treatment with Two Doses of Sulphadoxine-Pyrimethamine in Malaria Infection and Its Associated Adverse Pregnancy Outcomes: A Systematic Review

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## ABSTRACT

Malaria in pregnancy is associated with a number of adverse pregnancy outcomes. As a result, Intermittent Preventive Treatment has been recommended as one of the means for reducing the burden of infection and adverse consequences associated with it. This paper aims to evaluate the effectiveness of 2-dose Intermittent Preventive Treatment with Sulphadoxine-Pyrimethamine (IPT-SP) in reducing the risk of these adverse events. A comprehensive literature search of experimental studies was conducted, restricted to papers published from the year 2000 onwards. Thirteen studies were included, each comparing a 2-dose IPT-SP with another regimen and /or placebo. The Cochrane risk of bias assessment tool was used to assess the quality of included studies and a qualitative synthesis was done. Two-dose IPT-SP showed a consistent superiority over Chloroquine. It also demonstrated non-inferiority to other anti-malarial drugs like mefloquine and proguanil which were considered as 'gold-standards'. Only higher doses of SP and Dihydroartemisinin-piperaquine, showed clear superiority over 2-dose SP. This study shows that the 2-dose IPT-SP is effective in reducing the incidence of malaria in pregnancy and its adverse pregnancy outcomes. This effectiveness is complimented by its relative safety and ease of administration.

***Key Words:*** Malaria in pregnancy, intermittent preventive therapy, sulphadoxine-pyrimethamine, IPT, pregnancy outcome

## INTRODUCTION

Malaria is an infectious disease of high burden among pregnant women in sub-Saharan Africa. According to the World Health Organisation (WHO), an estimated twenty five million pregnancies are believed to occur in malaria-endemic regions of sub-Saharan Africa annually (WHO, 2004). Malaria in pregnancy could lead to adverse pregnancy outcomes like: maternal anaemia (Okafor et al., 2012); early pregnancy loss (Butler et al., 1997); low birth weight (Sirima et al., 2003); intra-uterine growth retardation; pre-term delivery; infant mortality (Steketee et al., 2001) and miscarriage (McGready et al., 2012). An estimated 75,000 to 200,000 infant deaths yearly have been attributed to malaria in pregnancy (Steketee et al., 2001). As part of measures to ensure protection against malaria infection and its adverse pregnancy outcomes, the World Health Organisation (WHO) recommends for all women in sub-Saharan Africa, the use of Insecticide Treated Nets (ITN); Intermittent Preventive Treatment (IPT) with Sulphadoxine-Pyrimethamine (SP); and prompt case management of malaria and anaemia during pregnancy (WHO, 2004).

Several studies have assessed the association between IPT use and pregnancy outcomes like malaria parasitaemia; cord

parasitaemia; low birth weight and pre-term labour; most of which have shown a lower risk for such events with receipt of Intermittent Preventive Treatment with Sulphadoxine-Pyrimethamine (IPT-SP). A cross-sectional study among 365 women in a Teaching hospital in South-eastern Nigeria revealed a lower prevalence of placental malaria (55.0%) among those who had received IPT-SP compared to those who had not (77.6%) (Ezebialu et al., 2012). Another cross-sectional study among 437 women who delivered at a tertiary centre in Maiduguri revealed a higher odds of placental malaria for non-usage of IPT (OR=3.15; 95% CI: 1.48-6.69) (Bako et al., 2009). A cross-sectional study involving 4,200 women attending a tertiary centre at Ekiti, Nigeria revealed a significantly lower birth weight among those who had not received IPT-SP compared to those who had received it (3.138kg ± 0.402kg versus 3.263kg ± 0.398kg (Peter et al., 2013).

A study at an antenatal clinic in Osogbo, Nigeria revealed a significant overall decline in malaria parasite density among the pregnant women after taking IPT-SP from 700±221.3, 629.3±196.3 and 556.6±165.8 to 37.8±25.6, 39.2±28.3 and 32.9±32.6 in the primi-gravidae, secundi-gravidae and multi-gravidae respectively (Adebayo et al., .2011). A cross-sectional study among 872 pregnant women in Ghana revealed that the odds of having sub-microscopic malaria was also lower among those who had received IPT compared to those who had not (0R=0.11; 95% CI: 0.02-0.22) (Nwaefuna et al., 2015). A study among 435 women who delivered at two health facilities at Mansa, Zambia revealed a significant difference in low birth weight among pauci-gravid women who had received 2 or more doses of IPT-SP compared to those who had received only a single dose or none at all (PR=0.33; 95% CI: 0.12-0.91). There was also a lower risk of pre-term delivery (OR=0.28; 95% CI: 0.13-0.60) among multi-gravid women who had received 2 or more doses of IPT compared to those who had received only a single dose or none at all (Mace et al., 2015).

A cross-sectional study in Imo, Nigeria among 432 women , out of whom 63.3% had received IPT, revealed a lower odds of having low-birth weight among those who had received IPT compared to those who had not (0R=0.70; 95% CI: 0.55-0.89) (Uwakwe et al., 2015). A cross-sectional study in Korle-Bu, Ghana among 363 women revealed lower odds for anaemia (0R=0.20; 95% CI: 0.12-0.34) and malaria (OR=0.18; 95% CI: 0.08-0.37) among those who received IPT compared to those who did not (Wilson et al., 2011). A multi-centre cross-sectional study in Cote d'Ivoire involving 1317 women revealed lower odds of having low birth weight babies among those who received IPT-SP. The lowest risk was among those who had received 3 doses and above (OR=0.24; 95% CI: 0.07-0.85); followed by those who had received only a single dose (OR=0.54; 95% CI: 0.31-0.96). There was however, no significant difference among those who had received 2 doses (OR=0.70; 95% CI: 0.44-1.12) (Toure et al., 2014).

A retrospective cohort study among 983 women in Ibadan comparing those who received IPT-SP with those who received Pyrimethamine and those who did not receive any chemoprophylaxis revealed a prevalence of pre-term delivery of 10.5%, 19.2% and 25.3% respectively for the three groups. Also, the mean birth weights of the three groups were significantly different thus: 3204g ± 487.16g, 3075g ± 513.24g and 3074g ± 505.92g respectively (Folade et al., 2007). In an observational cohort of 4,200 women doing their antenatal care at a tertiary centre at Ekiti, Nigeria, there was a statistically significant lower birth weight among babies born to those who had not received IPT-SP compared to those who had received it (3.138±0.402 versus 3.263±0.398) (Aduloju et al., 2013). Another observational cohort study in Malawi involving 448 women revealed IPT-SP to be effective in significantly reducing the prevalence of sub-microscopic malaria

infection among already infected persons at their next visits (23.9% versus 48.5%). However, it was not effective in preventing the incident cases among those who were initially negative as noticed by a similar rate of infection between those who received IPT and those who did not (2.0% versus 2.2%; *p*=0.83) (Cohee et al., 2014).

A hospital-based cohort study in Kenya assessing the effectiveness of IPT-SP in 2,302 deliveries revealed that 1 dose or above of SP was effective in reducing placental malaria (OR=0.56; 95% CI: 0.39-0.83) and low birth weight (OR=0.65; 95% CI: 0.45-0.95). Also, there was an adjusted increase in birth weight of 61g (95% CI: 22-101g) for each increase in number of SP doses (Eijk et al., 2004). A retrospective cohort study among 703 pregnant women in Malawi revealed that IPT-SP had a dose-dependent effect on reducing adverse composite birth outcomes, with adjusted prevalence ratios of 0.5(95% CI: 0.3-0.82); 0.3 (95% CI: 0.19-0.48) and 0.18 (95% CI: 0.05-0.61) for 1 dose, 2 doses and 3 doses respectively compared to those who had not received any (Gutman et al., 2013).

Even though these studies favour the use of IPT-SP, they do not form the highest form of evidence since these study designs are prone to several biases. For establishing evidence, systematic reviews of well conducted randomized controlled trials (RCT) are the gold standard. The aim of this review is to evaluate the effectiveness of 2-doses of IPT with SP in reducing the incidence of malaria parasitaemia and its adverse outcomes among pregnant women.

## MATERIALS AND METHODS

Literature was reviewed systematically by conducting a comprehensive search in Science Direct, Google scholar, PubMed and Cochrane libraries. The criteria for including a study for review were:

a. To be a randomized controlled trial.
b. Participants should be pregnant women.
c. The intervention/comparator should be intermittent preventive treatment with two doses Sulphadoxine-Pyrimethamine.

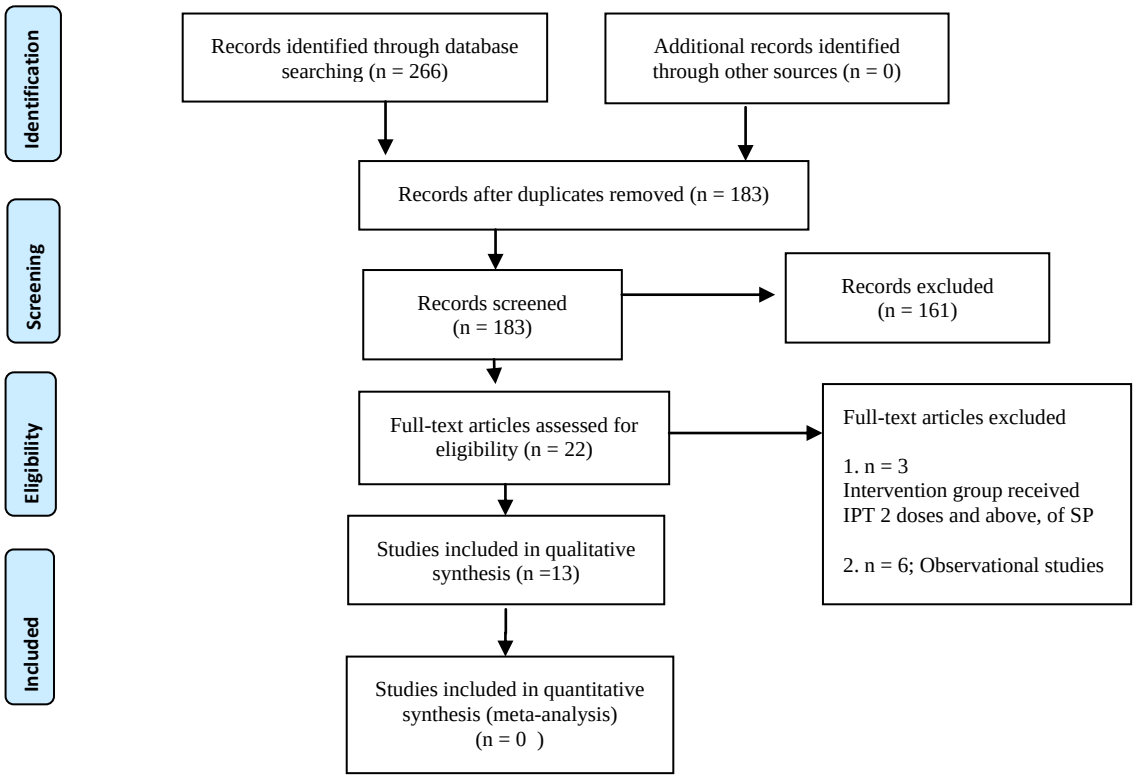


**Figure 1: Flow diagram for systematic review of studies**

Search terms included: intermittent preventive/prophylactic therapy/treatment; Sulphadoxine-Pyrimethamine, pregnancy and pregnant women. Search was restricted to articles published from the year 2000 onwards and those conducted in sub-Saharan Africa. A total of 105 articles were retrieved from the Cochrane library; 51 from Science Direct; 12 from Google scholar, and 98 from PubMed. The PRISMA flow diagram for the search strategy is shown in figure 1.

## RESULT

### Review

As illustrated in Figure 1, 226 articles were identified. They were screened based on their titles and abstracts; after which only 22 were fully reviewed. Six were excluded on the basis of being observational studies, while in another three; the intervention was two doses of SP or more. Thirteen studies were finally included, all of which were randomized controlled trials. These selected studies were scrutinized based on the type of study design, participants, intervention and the study outcomes. All selected studies were conducted in sub-Saharan Africa: 3 in Nigeria; 2 in Mali; 1 in Malawi; 2 in Burkina Faso; 1 in Mozambique; 1 in Kenya; 1 in Benin; 1 in Ghana, and 1 was a multi-centre study with samples drawn from Benin, Gabon, Mozambique and Tanzania.

**Table1: Quality Assessment of the Included RCTs**

| Study | Country | Randomization | Sequence generation | Allocation concealment | Blinding of participants | Blinding of assessors | Selective reporting | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|
| Maiga 2011 | Mali | Done | Done | Done | Done | Done | No | Low |
| Kyentao 2015 | Mali | Done | Not clear | Not clear | Not clear | Not clear | No | Not clear |
| Filler 2006 | Malawi | Done | Done | Not clear | Not done | Done | No | Moderate |
| Jeremiah 2012 | Nigeria | Done | Not clear | Done | Done | Not clear | No | Not clear |
| Omole-Ohonsi 2011 | Nigeria | Done | Not clear | Not clear | Not clear | Not clear | No | Not clear |
| Menandez 2008 | Mozambique | Done | Done | Done | Done | Not clear | No | Low |
| Asa 2008 | Nigeria | Done | Not clear | Not clear | Not clear | Not clear | No | Not clear |
| Gonzalez 2014 | Multi-centre | Done | Done | Not clear | Not clear | Not clear | No | Not clear |
| Tiono 2009 | Burkina Faso | Done | Done | Done | Done | Not clear | No | Low |
| Valea 2010 | Burkina Faso | Done | Done | Not clear | Not clear | Not clear | No | Not clear |
| Desai 2015 | Kenya | Done | Done | Not clear | No | Done | No | High |
| Tagbor 2010 | Ghana | Done | Done | Done | Done | Done | No | Low |
| Briand 2009 | Benin | Done | Not clear | No | No | Done | No | High |

The Cochrane risk of bias assessment tool was used to assess the quality of the thirteen included studies and the results are presented in Table 1. None of these studies seemed to have had any selective reporting of outcomes. Only the studies by Maiga et al. (2011) and Tagbor et al. (2010) had explicitly stated out its sequence generation and that allocation concealment; blinding of participants and blinding assessors had been done.

**Table 2: Data Extraction Table**

| Study details and design | Participant details | Intervention/ comparators | Outcomes/ analyses | Results |
|---|---|---|---|---|
| 1.Maiga et al., 2011<br>Study design: RCT | ANC Attendee;<br>All gravidae | Intervention: 3-doses SP<br>Comparator: 2-doses SP | 1.Placental malaria;<br>2.Low birth weight;<br>3. Preterm delivery | 1. (APR=0.48; 95% CI: 0.32-0.71);<br>2. (6.6% versus 13.3%; APR=0.50 (0.32-0.79);<br>3. (3.2% versus 8.9%; APR=0.37; 95% CI: 0.19-0.7) |
| 2. Kyentao et al., 2005<br>Study design: RCT | ANC Attendee;<br>Primi- & secondi-gravidae | Intervention: 2-doses SP<br>Comparator: weekly CQ | 1.3rd trimester anaemia*<br>2.Lower birth weight*<br>3.Placental malaria*<br>4. Pre-mature delivery | 1. OR=0.49 (0.36-0.68)<br>2. 0R=0.69 (0.49-0.98)<br>3. OR=0.69 (0.48-0.98)<br>4. 0R=1.15 (0.44-3.04) |
| 3. Filler et al<br>Study design: RCT | ANC Attendee;<br>Primi- and secundi-gravidae | Intervention: 2-doses of SP<br>Comparator: monthly SP | 1.Placental malaria** | 1. RR=0.37 (0.11-1.19) |
| 4. Jeremiah et al., 2012<br>Study design: RCT | ANC Attendee;<br>All gravidae | Intervention: 2-doses of SP<br>Comparator: daily proguanil | 1.Parasitaemia**<br>2.Pre-term**<br>3.Cord parasitaemia**;<br>4.Low-birth weight** | 1. p=0.429<br>2. p=0.262<br>3. p=0.385<br>4. p=0.175 |
| 5. Omole-Ohonsi et al., 2014<br>Study design: RCT | ANC Attendee;<br>Primigravidae | Intervention: 2-doses of SP<br>Comparator: daily proguanil | 1.Malaria parasitaemia**<br>2.Haematocrit level** | 1. p=0.388<br>2. p=0.074 |
| 6. Menandez et al., 2008<br>Study design: RCT | ANC Attendee;<br>All gravidae | Intervention: 2-doses of SP<br>Comparator: placebo | 1.L.B.W. **<br>2.Pre-term delivery**<br>3.Cord parasitaemia** | 1. RR=0.90 (0.68-1.40)<br>2. RR=0.372 (0.39-1.89)<br>3. OR=0.738 (0.22-2.96) |
| 7. Asa et al., 2008<br>Study design: RCT | ANC Attendee;<br>Primi- and secundi-gravidae | Intervention: : 2-doses of SP<br>Comparator: CQ | 1.Anaemia protective efficacy* | 1.OR=0.5 (0.29-0.85) |
| 8. Gonzalez et al., 2014<br>Study design: RCT | ANC Attendee;<br>All gravidae | Intervention: 2-doses of SP<br>Comparator: Mefloquine | 1.L.B.W.<br>2.Parasitaemia<br>3.Anaemia | 1. RR=0.98 (0.82-1.16)<br>2. RR=1.43 (1.04-1.81)<br>3. RR=1.09 (0.96-1.176) |
| 9. Tiono et al., 2009<br>Study design: RCT | ANC Attendee;<br>All gravidae | Intervention: 2-doses of SP<br>Comparator: CQ | 1.L.B.W.*<br>2.Placental malaria<br>3.Parasitaemia* | 1. OR=0.38 (0.19-0.72)<br>2. OR=0.75 (0.4-1.41)<br>3. p<0.001 |
| 10.Valea et al., 2010<br>Study design: RCT | Community<br>All gravidae | Intervention: 3-doses of SP<br>Comparator: 2-doses of SP | 1.Anaemia<br>2.Severe anaemia<br>3.L.B.W.<br>4.Stillbirth<br>5.Spontaneous abortion | 1. IRR=0.99 (0.88-1.12)<br>2. IRR=0.38 (0.16-0.90)<br>3. IRR=0.92 (0.69-1.24)<br>4. IRR=1.64 (0.74-3.61)<br>5. IRR=1.36 (0.74-2.53) |
| 11. Tagbor et al., 2010<br>Study design: RCT | ANC Attendee;<br>All gravidae | Intervention: RDT screening + treatment with Artesunate and Amodiaquine<br>&<br>RDT screening + SP treatment<br>Comparator: 2-doses of SP | 1. 3rd trimester severe anaemia**<br>2.L.B.W. **<br>1. 3rd trimester Severe anaemia**<br>2.L.B.W. ** | 1. RR=1.15 (0.54-2.44)<br>2. RR=1.16 (0.89-1.51)<br>1. RR=1.31 (0.63-2.75)<br>2. RR=0.87 (0.65-1.15) |
| 12. Briand et al., 2009<br>Study design: RCT | ANC Attendee;<br>All gravidae | Intervention: 2-doses SP<br>Comparator: Mefloquine 2-doses | 1.Placental malaria*<br>2.L.B.W.<br>3.Hb level | 1. RR=0.38 (0.19-0.74)<br>2. RR=0.81 (0.59-1.13)<br>3. +0.13 (-0.05-+0.31) |
| 13. Desai et al., 2015<br>Study design: RCT | | Intervention:<br>IPT with Dihydroartemisinin–piperaquine Comparator:<br>a. Intermittent screening + treatment with Dihydroartemisinin–piperaquine<br>b. IPT with 2-doses SP | 1.Malaria infection<br>2.Clinical malaria | 1. IRR=0·28 (0·22–0·36)<br>2.IRR=0·16 (0·08–0·33) |

Note: (*) significant in favour of 2-dose SP; (**) non-inferiority of 2-dose SP; (a) non-inferiority of 2-dose SP L.B.W. (low birth weight); APR (Adjusted prevalence ratio); OR (Odds ratio); RR (Relative risk); IRR (Incidence rate ratio)

Table 2 above shows a summary of the findings from the thirteen included studies. With regards to the outcomes reported in these studies, two doses of Sulphadoxine-Pyrimethamine (SP) had consistently shown superiority over Chloroquine (Kyentao et al., 2005; Asa et al., 2008; Tino et al., 2009); while other antimalarial drugs like Proguanil and Mefloquine did not show any statistically significant difference in outcomes from it (Jeremiah et al., 2012; Omole-Ohonsi et al., 2014; Gonzalez et al., 2014). Even intermittent screening followed by treatment of positive cases with Amodiaquine, Artesunate or SP did not show superiority over IPT with 2-dose SP (Tagbor et al., 2010). However, IPT with three doses of SP (Maiga et al., 2011; Valea et al., 2010) as well as Dihydroartemisinin-piperaquine (Desai et al., 2015) showed clear superiority over two doses of SP.

**Qualitative synthesis**

The outcomes used for comparing the effectiveness of the drugs used for intermittent preventive treatment in these studies though different, are all conceptually-related. They are: malaria parasitaemia; placental parasitaemia; cord parasitaemia; maternal anaemia; spontaneous abortion; low birth weight and pre-term delivery. Chloroquine, Mefloquine, Proguanil, placebo and even different dosing of SP had been used as comparators. The conventional 2-doses of SP had shown consistent superiority over various regimens of Chloroquine (Kyentao et al., 2005; Asa et al., 2008; Tino et al., 2009). Proguanil (Jeremiah et al., 2012; Omole-Ohonsi et al., 2014) and Mefloquine (Gonzalez et al., 2014) which the researchers considered as gold standards and even likely alternatives to the conventional IPT-SP did not show any superiority over it even though both have higher frequencies of administration. In the placebo controlled trial by Menandez et al. (2008), two doses of SP did not show any superiority over placebo in reducing adverse malaria health outcomes. However, since both groups had used Insecticide Treated Nets (ITN), its protective effect is likely to have obscured the effects of the IPT and as suggested by the researchers, a prudent adoption of ITN may decrease the need for malaria prophylaxis during pregnancy.

## DISCUSSION

The two-dose regimen of SP seems to be both an effective and efficient drug of choice for IPT. This is because from studies so far, only the three-dose regimen of SP has shown superiority in reducing malaria-associated adverse pregnancy outcomes over the conventional two doses. Other drugs with similar levels of effectiveness are associated with more frequent dosing. This dual characteristic of effectiveness and lesser dosing makes SP the drug of choice for IPT, considering the fact that malaria is basically endemic in low resource regions of the world which in turn implies less access to health facilities making a drug with less frequent dosing more favourable.

Compliance is likely to reduce with higher frequency of dosing as has been reported by the Nigerian National Population Commission (NPC) among pregnant women in Borno State aged 15-49 years, that for IPT with SP, only 13.9% had received any dose during their pregnancy, 6.7% had received 2 doses or more while only 1.9% had received 3 doses (NPC, 2013). Considering this fact that from one dose to three, compliance could drop so drastically from 13.9% to 1.9%, a drug with daily dosing like Proguanil is unlikely to be a suitable alternative considering that it has no superior protective effects over SP.

The study by Menandez et al. (2008) which revealed no statistical difference in the outcomes between those who received two doses of SP and those who received placebo should not be seen as a write-off over SP but rather as one which shows the potency of ITNs. If both groups had adhered strictly to the use of ITNs and as a result had received the desired protection from ITN use, then the pure effects of IPT in such a case would be hard or even impossible to

measure. Besides, other studies have revealed a clear superiority of the two-dose SP regimen over placebo for IPT. A systematic review which incorporated 4 studies comparing 2-doses of IPT-SP with case management or placebo in the first or second trimester of pregnancy revealed a lower risk with IPT-SP for placental malaria (RR: 0.48; 95% CI: 0.35-0.68); low birth weight (RR: 0.71; 95% CI: 0.55-0.92); and anaemia (RR: 0.90; 95% CI: 0.81-0.99) (Kulie et al., 2007).

Another plus to the use of SP for IPT is that its mode of delivery did not matter but rather receipt of the IPT-SP itself, as shown in a study in Uganda involving 2,785 pregnant women comparing those who had received IPT-SP at community levels and those who received it from health centres. In that study, the incidence of low birth weight was lower among those who had received IPT-SP at the community level (6.0% versus 8.3%) just as their level of coverage for first dose of IPT-SP was higher during their second trimester, compared to those who had received it at the health centre (92.4% versus 76.1%) (Mbonye et al., 2008). Even though Dihydroartemisinin-piperaquine had shown a superior outcome compared to 2-dose SP (Desai et al., 2015), it is advisably better to hesitate its adoption as an IPT choice because being a treatment of choice by virtue of being an Artemisinin-based combination therapy (WHO, 2015), its wide use as a preventive treatment is likely to speedy the development of resistant for these drugs.

It can therefore be recommended for the meantime from this review, that two doses of SP to be used for IPT, and if any alternative should be considered, it should be the three dose regimen of SP. It is also recommended that IPT with SP be started early. The difference in effectiveness between IPT given early (at 4 months) and given late (at 7 to 8 months) was studied by a synthesis of two studies conducted in Benin Republic (a randomized controlled trial and a cohort study) involving a total of 1,439 women. The results showed that receiving IPT early was associated with about a half lower risk of low birth weight compared to receiving it late (OR=0.5; 95% CI: 0.3-0.9) (Huynh et al., 2012).

## CONCLUSION AND RECOMMENDATION

The use of 2-doses of IPT-SP has demonstrated good ability in significantly reducing these adverse outcomes. This advantage is further buttressed by its relative safety and ease of administration. It is therefore recommended to be the drug of choice for preventive treatment of malaria for now before more effective and efficient drugs are discovered.

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