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Meta-analysis of intermittent treatment with sulfadoxine-pyrimethamine in pregnancy in malaria endemic areas

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META – ANALYSIS OF INTERMITTENT TREATMENT WITH SULFADOXINE - PYRIMETHAMINE IN PREGNANCY IN MALARIA ENDEMIC AREAS

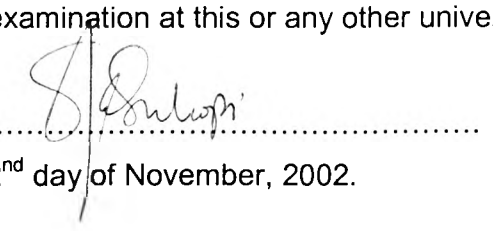
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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree
of
Master of Science in Medicine in Epidemiology and Biostatistics

Johannesburg, 2002.

DECLARATION:

I, Abdallah Bakari Mkopi declare that this research report is my work. It is being submitted for the degree of Master of Science in Medicine in the branch of Epidemiology and Biostatistics in the University of the Witswatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



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2nd day of November, 2002.

ABSTRACT:

Objective – To systematically evaluate the efficacy of double dose of sulfadoxine-pyremithamine (SP/SP) treatment in pregnancy in malaria endemic areas.

Methods - The relevant articles were retrieved by a computerized search of Medline, Cochrane Review, Pub Med and Google with the following key words, sulfadoxine-pyrimethamine, intermittent, pregnancy, Quasi-experimental studies and Randomised Control Trials. Three reviewers identified only 2 papers meeting the inclusion criteria set for the study. Systematic quantitative review was performed.

Results – 2 papers were included in the meta-analysis. The protective efficacy of SP/SP on peripheral parasitaemia was 86% (95% CI 88%, 91%) with risk ratio (RR) of 0.14 (95% CI 0.09, 0.22). The protective efficacies of SP/SP on placental parasitaemia and severe anaemia were 56%(95% CI 29%, 73%) and 39% (95% CI 16%, 55%) respectively. No significanct efficacy of SP/SP was shown on low birth weight (LBW) outcome.

Conclusion – Limited available information show that SP/SP treatment during pregnancy has a positive impact on peripheral parasitaemia, placental parasitaemia and severe anaemia, such an effect not clearly demonstrated for LBW. Therefore, Further evidence is required to fully describe the efficacy of SP/SP in pregnancy.

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1.0 INTRODUCTION:

1.1 Malaria burden in general;

Malaria is the most public health problem facing over 2.4 billion people in over 90 countries. It is the major cause of death and morbidity. About 200-300 million clinical cases of malaria occur annually with mortality of one million people (1). Approximately 90% of these deaths occur in Sub-Saharan Africa (2).

In Sub-Saharan Africa malaria is mainly stable with high or moderate transmission in many areas. Other areas e.g. East Africa high lands, Zimbabwe, South Africa; malaria is unstable with low transmission and potential for epidemic (3).

1.2 Malaria in pregnancy:

Each year, approximately 24 million African women become pregnant in malaria-endemic areas, and they are at risk of malaria infection during pregnancy (4). It is common knowledge that pregnant women are more susceptible to infection of many diseases, which may be serious, and life threatening (5). Pregnant women are the most risk group to contact malaria. When a woman is pregnant her immunity is reduced, making her more vulnerable to malaria with dangerous consequences for mother and her child (6). That is why the prevalence of malaria higher among pregnant as compared to non-pregnant women (7). The effects of malaria to women are greatest in their first pregnancy (primigravidae), but they do extend into their second or even third pregnancy.

1.3 The epidemiology of malaria in pregnancy in Africa:

The epidemiology of malaria in pregnancy differs greatly with the women's pre-existing level of immunity to the malaria. This depends largely on whether

malaria transmission is high to moderate transmission (Stable Malaria) or low transmission (Unstable Malaria) (1). In areas with intense stable transmission (e.g. large part of Sub-Saharan Africa); malaria is often asymptomatic (occasionally mild fever), severe maternal anaemia is common, peripheral parasitaemia often at low level, placental infection is common and often heavy and the effects on the foetus lead to cause low birth weight (8).

Areas with unstable malaria (e.g. endemic parts of southeast Asia, South America); the effects of malaria in non-immune pregnant women include; uncomplicated malaria with high fever, severe malaria with high risk of maternal and foetal death, abortion, stillbirth, and LBW (9). This also include severe malarial anaemia is a common and very dangerous complication in pregnancy (10, 11)

1.4 The clinical consequences of malaria infections in pregnancy:

The consequences of malaria infections in pregnant women consist of maternal and fetal effects. The maternal effects include severe anaemia, cerebral malaria, Hypoglycaemia, pulmonary oedemal, high fever and placental infection. The fetal effects include low birth weight, abortion, congenital malaria and fetal malaria (12).

This review looks at consequences of anaemia, low birth weight, peripheral infection and placental infection in pregnant women.

Anaemia in pregnancy is usually multifactorial. The main causes of anaemia among women in Sub-Saharan Africa are malaria, iron deficiency, folate

deficiency, sickle cell disease and advanced HIV disease (12, 13, 14). Malarial anaemia is not primarily iron deficiency anaemia because the mechanism for anaemia in malaria causes destruction of red blood cells which releasing haemoglobin from the body, which may be excreted through the urine (15).

Generally, maternal deaths due to malaria are caused by severe anaemia in high transmission areas although other complications of severe malaria (e.g. cerebral malaria, pulmonary oedema) are also occur in this setting and many women enter labour with dangerously low haemoglobin (15, 16). According to WHO report of 1993 over 50% of pregnant women in Sub-Saharan Africa may be anaemic (Hb < 11g/dl) and 5-15% have severe or very severe anaemia (Hb < 7g/dl) (17). Pregnant women with severe anaemia at any level of malaria transmission are at great risk of mortality from obstetric haemorrhage and heart failure (13, 15).

Other effects are peripheral and placental malarial parasitaemia. It has been reported that women with the first pregnancy usually have a higher prevalence of malaria infection (peripheral or placenta) as compared to the women that have had pregnancies before (18). Malaria infection of the placenta is a major contributor to low birth weight (LBW)(19).

The LBW (<2500g) is the greatest single risk factor for neonatal and early infant death (20). In African primigravidae one in four babies has low birth weight and malaria may be the cause of low birth weight up to 50% of deliveries (21). The relative risk for low birth weight is associated with women who experience pregnancy for the first time (22). Low birth weight is also associated with significant increased risk of neonatal and infant morbidity.

Other underlying causes of low birth include maternal anaemia and high fever (1). At all levels of transmission, malaria during pregnancy especially in primigravidae is associated with low birth weight.

1.5 The impact of malaria in pregnancy on communities and health Services in Africa:

Malaria in pregnancy is associated with increase morbidity and mortality, which occur among women, mainly in Africa, Table 1. Data from Angola and Mozambique have shown maternal mortality rate of 1,500 per 100,000 births in both (23). It is estimated that 20% of all maternal deaths are due to severe anaemia during pregnancy (13). The pregnant women at risk of malaria are also substantial, for example in 1990 it counted 1,191,600 pregnant mothers were at risk of malaria in Tanzania (23).

Table 1: Maternal Mortality and the Malaria burden (23)

Country	No. of pregnant women at risk	Maternal mortality rate per 100,000 births (1990)
Angola	568,000	1,500
Botswana	21,600	250
Malawi	493,000	560
Mozambique	682,000	1500
Namibia	38,940	370
South Africa	131,100	230
Swaziland	10,200	560
Tanzania	1,191,600	770
Zambia	368,000	940
Zimbabwe	219,000	570

Generally, morbidity due to malaria overburdens the health system in African countries. For instance, in Tanzania malaria morbidity has been reported as a leading cause of outpatient consultations accounting from 24.8% to 42.2% of the outpatient cases in 1991 (24).

The costs for control and treatment of malaria are also extremely high, it has been estimated that malaria cost over US$ 2 billion to the economy in Africa alone annually (25).

Malaria also contributes to a considerable burden in endemic communities with premature deaths, disability from illness and it impedes on social and economic development (26).

1.6 Treatment and preventive measure of malaria in pregnancy:

It goes without saying that pregnant women need preventive and curative care in order to prevent or reduce maternal and infant mortality together with reduction of economic burden of malaria. Control of falciparum malaria in pregnancy depends on the level of transmission and it is based on a combination of prompt and effective treatment of symptomatic malaria, anaemia and peripheral parasitaemia. It is also based on prevention of malaria by chemoprophylaxis or intermittent treatment, regular screening and personal protection to prevent vector contact e.g. use of Insecticide treated bed nets (27).

World Health Organisation (WHO) recommends that for pregnant women in low transmission areas, an effective antimalaria drug should be provided on regular basis (28).

In highly endemic areas, WHO recommends intermittent treatment with an effective preferably one-dose of antimalarial drug should be available to women during the first and second trimester. Such intermittent treatment should be started from second trimester onwards and be given at intervals of not less than one-month (29).

The choice of drug for chemoprophylaxis or intermittent treatment in pregnancy should base on the drug efficacy, parasite resistance, drug cost, risk from malaria and adverse effects of prophylaxis (30).

Chloroquine (CQ) treatment was the chemoprophylaxis drug most widely used in Africa. As a consequence of this observation, Malawi, Kenya and

Tanzania replaced CQ for malaria control in pregnancy with two treatment doses of SP in 1993, 1997 and 2001 respectively. The efficacy of CQ treatment declined rapidly during the 1980s (31).

The WHO advocates sulfadoxine-pyrimethamine (SP) for treatment in pregnancy of falciparum malaria resistant to CQ (32).

1.7 Questions to be addressed in this study:

The current practice of malaria control in some of African countries is using SP as the first-line antimalarial drug. These countries are Botswana, Kenya, Malawi, South Africa, Tanzania and Zambia. In these countries intermittent treatment during pregnancy is advocated. As more countries in malaria endemic areas consider changing their own antimalarial programmes from CQ to SP treatment during pregnancy, the evaluation of the effectiveness of this new SP intermittent treatment policy is essential for control malaria in pregnancy.

Studies have shown that SP intermittent treatment seems to be effective in preventing some of the consequences of malarial infection in pregnant women compared to CQ treatment (33). It has been agreed that SP treatment is useful for malarial infections with some chloroquine-resistance *P.falciparum* compared to chloroquine (34). However, it is not recommended to use SP before 16th week of pregnancy because of concerns on possible abnormalities in the fetus (35). One report reveals that the evidence of SP intermittent treatment on birth weight is weak (36). The side-effects of SP are rash, agranulocytosis, aplastic anaemia, thrombocytopenia, hypersensitivity,

erythema, Steven Johnson's syndrome, exfoliative dermatitis, glossitis, convulsions, headache, ataxia, hallucinations, tinnitus and hemolysis in G6PD deficiency (37). It has been reported from Mali that there is no significant difference in the rates of placental parasitaemia or low birth weight babies among women who received SP or CQ, in this area with chloroquine sensitive to *P.falciparum* malaria (38). Also, there are some indications that, chemoprophylaxis with chloroquine during pregnancy may have a protective effect, even in certain areas where chloquine-resistant *P.falciparum* is endemic (39). Therefore a meta-analysis has been undertaken on SP intermittent treatment studies in pregnancy so as to collate information on the benefit of this intervention on health outcomes. For this meta-analysis the following outcomes have chosen to evaluate the efficacy of SP intermittent treatment during pregnancy on;

(i) Severe anaemia in pregnant women.
(ii) Peripheral parasitaemia in pregnant women.
(iii) Placental parasitaemia in pregnant women.
(iv) Occurrence of low birth weight babies.
(v) Side effects in pregnant women.

2.0 METHODS:

2.1 Search Strategy:

A computerized search of Medline, Cochrane Review, Pub Med and Google with the following key words; sulfadoxine-pyrimethamine, intermittent, pregnancy, Quasi-experimental studies and Randomised Control Trials retrieved the relevant articles. Published and unpublished relevant articles from January 1990 to December 2000 were used. Unpublished articles were used in order to avoid publication bias. The references of all identified relevant studies including reviews and meta-analyses were searched again in computer or hand searched in the Libraries for additional potential relevant publication. Also for the articles that were not found in full text respective authors were contacted.

2.2 Selection criteria:

Studies that were included in the systematic quantitative review met the following criteria;

- The comparison of treatment was SP/SP with CQ/CQ or placebo and not both (SP/CQ). The above comparison was selected because it is recommended schedule used in Tanzania, Malawi, Kenya and other countries.
- Strength of the effect between treatment and control group was tested.
- The study design was Randomised Control Trials and Quasi-experimental studies.
- Reports were in English only.
- Published and unpublished studies conducted from 1990 to 2000.

2.3 Quality assessment:

A method for assessing the quality of a randomised control trial was used for all studies that were included in the study review (40).

All selected studies were assessed based on the following checklist;

- Was the allocation to the treatment groups really random?
- Was the treatment allocation concealed?
- Were the groups similar at baseline in terms of prognostics factors?
- Were the eligible criteria specified?
- Were outcome assessors blinded to the treatment allocation?
- Was the care provider blinded?
- Were the point estimates and measure of variability presented for the primary outcome measure?
- Data for at least one key outcome was analysed by "intention to treat"?

2.4 Data extraction:

For each of the study articles, three different reviewers one being a clinician extracted the following details.

- Study country

  The name of country where the study was conducted was noted.

- Study date

  The starting and finishing dates were jotted down.

- Study design

  The study design was Randomised Control Trial or Quasi-experimental study.

- Setting

  The information on area where the study conducted was collected, based on malaria epidemiological and rural/urban areas.

- Sample size

  The sample size of the study subjects was noted.

- Lost to follow-up

  This is the number of study subjects who dropped out during the study.

- Participants

  The women with their first or multiple pregnancy and gestation period were written down.

- Reported antimalarial regimens/ Intervention given

  The intervention given during the study was noted; this was sulfadoxine-pyrimethamine, chloroquine or placebo depended on gestation at recruitment.

- Comparison regimens (Interested in the review)

  The information collected here was only interested in this review; that is, the comparison of treatment was SP/SP (two-dose SP, with treatment doses – 1500 mg sulfadoxine and 75 mg pyrimethamine – at enrolment and again early in the third trimester) and CQ/CQ (an initial treatment dose of CQ – 25 mg base/kg given as divided dose over a three-day period at enrolment followed by CQ – 300 mg base weekly until delivery) or placebo not both (SP/CQ). I selected these kinds of doses-interventions as recommended by WHO (29, 30, 32).

- Outcome measures at delivery for comparison regimens.

  The outcome measures to assess efficacy of sulfadoxine-pyrimethamine over chloroquine/placebo were recorded for comparison.

- Side effects

  The adverse effects of sulfadoxine-pyrimethamine to pregnant women during the study were noted.

- Comments

  Any significant information relevant to data extraction on individual study was noted down.

2.5 Data Analysis:

In order to avoid of the biased choice of published estimates, it was decided to calculate the actual estimates of risk ratios and protective efficacy with 95% confidence intervals using crude data as the authors presented them. Before calculating the protective efficacy, the Risk Ratio (RR) with 95% confidence intervals was determined to indicate comparison effect between women of those getting SP/SP and Chloroquine/Placebo in relation to failure and success in malaria prevention. Thereafter a calculation of the protective efficacy of double dose - sulphadoxine-pyrimethamine (SP/SP) compared with chloroquine/placebo at delivery was performed using the following formula;

Protective efficacy = 100 x (1 – Risk Ratio).

The studies were considered in individual (without meta-analysis) and group (with meta-analysis) form for the calculation of risk ratios and protective efficacy with 95% confidence intervals.

The intercooled STATA 7.0 package was used to perform the estimates with graphical displays. The statistical significance was tested by the method of Mentel and Haenszel. This is a recommended method of summarizing results from several studies (41).

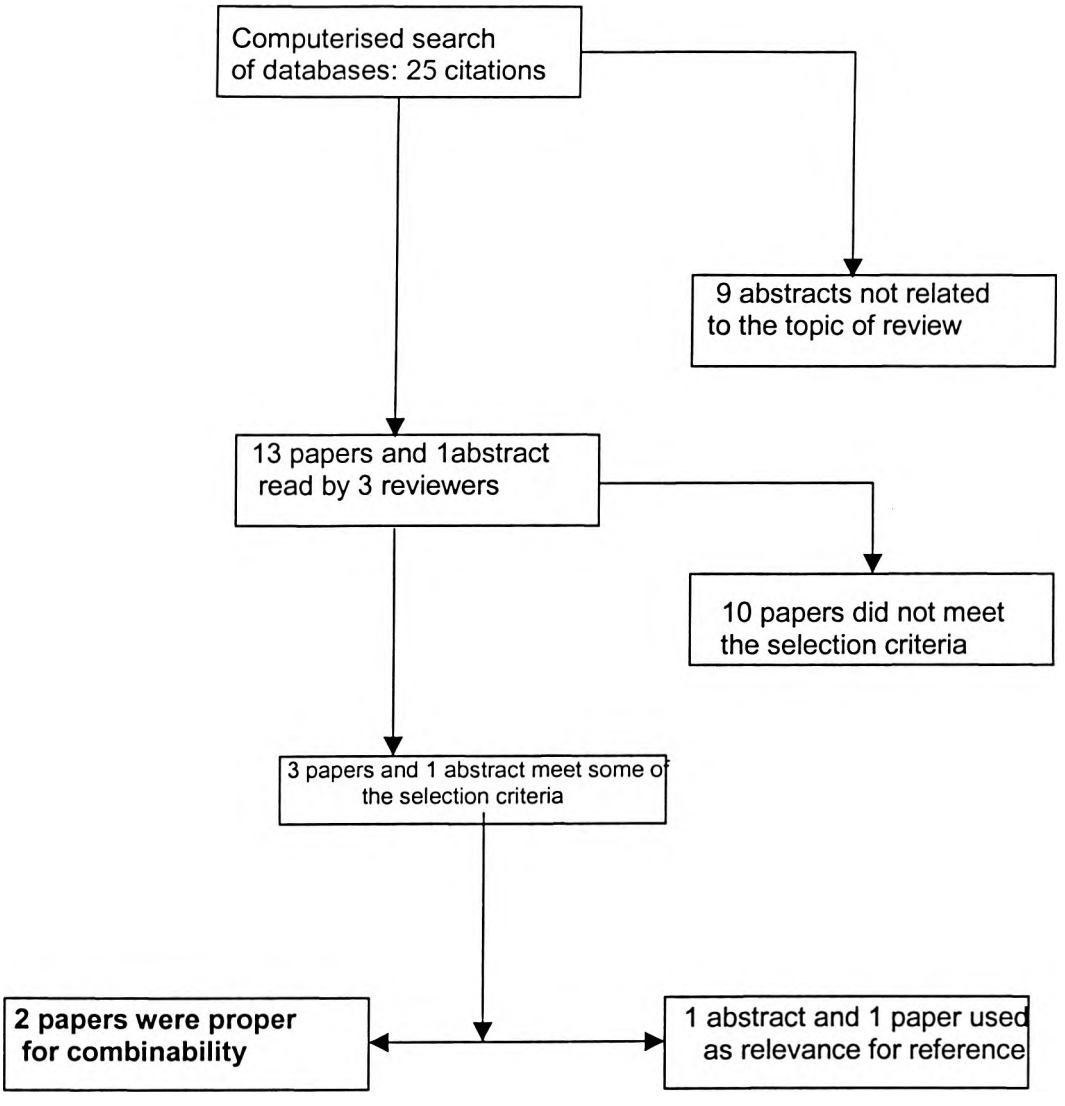
3.0 RESULTS:

3.1 Search outcomes:

The search of the computerised databases identified a total of 25 citations. After checking for doubles, and excluding studies clearly not related to the objective of our review, 13 papers and 1 abstract were considered in the selection procedure. Furthermore, looking on the inclusion criteria, 2 papers were finally included in the review. Efforts were made to secure full text of in study from Mali but in vain only abstract were obtained. Disagreements between the reviewers on individual items were identified and resolved during a consensus meeting. After 3 papers and1 abstract were properly reviewed and based on quality assessment only 2 papers were found to be proper for quantitative analysis, on the assumption that chloroquine and placebo has the same effect in an area where chloroqune-resistant *P. falciparum* is endemic. The rest citations were remained as relevant references.

The following flow diagram presents the number of abstracts and papers accepted and rejected by the three reviewers during the selection procedure.

Figure 1: Flow diagram of papers accepted and rejected:



Therefore, based on checklist above, and summary of selected studies, the differences in study designs and settings across two selected studies can indicate that the results of some studies were more likely to be affected by bias than others. These studies were done in Kenya and Malawi. No study outside Africa was found that met inclusion criteria.

The following table indicates a summary of quality assessment. Table 2 shows that study 1 was properly conducted as it fulfils all assessment criteria compared to study 2.

Table 2: Quality assessment of two trials included in a systematic review.

Assessment criteria	Study 1	Study 2
Was the allocation to the treatment groups really random?	Yes	No
Was the treatment allocation concealed?	Yes	No
Were the groups similar at baseline in terms of prognostics factors?	Yes	Yes
Were the eligible criteria specified?	Yes	Yes
Were outcome assessors blinded to the treatment allocation?	Yes	No
Was the care provider blinded?	Yes	No
Were the point estimates and measure of variability presented for the primary outcome measure?	Yes	Yes
Data for at least one key outcome was analysed by "intention to treat"?	Yes	No
Total Score	**8/8**	**3/8**

3.2 Table of results for data analysis:

(a) Presented without meta-analysis

Table 3: The outcome for peripheral parasitaemia in each trial:

Study	SP group (n/N)	Control group (n/N)	RR (95%CI)	Protective efficacy in %(95%CI)
1	19/350	134/377	0.15 (0.10, 0.24)	85% (76%,90%)
2	2/71	12/38	0.09 (0.02, 0.38)	91%(62%,98%)

Table 4: The outcome for placental parasitaemia in each trial:;

Study	SP group (n/N)	Control group (n/N)	RR (95%CI)	Protective efficacy in %(95%CI)
1	16/205	29/196	0.53 (0.30, 0.94)	47%(6%,70%)
2	6/71	12/38	0.27 (0.11, 0.66)	73%(34%,89%)

Table 5: The outcome for severe anaemia in each trial;

Study	SP group (n/N)	Control group (n/N)	RR (95%CI)	Protective efficacy in %(95%CI)
1	50/350	88/378	0.61 (0.45, 0.84)	39%(16%,55%)
2	-	-	-	-

Table 6: The outcome low birth weight in each trial;

Study	SP group (n/N)	Control group (n/N)	RR (95%CI)	Protective efficacy in %(95%CI)
1	-	-	-	-
2	12/71	10/38	0.64 (0.31, 1.35)	36%(-35%,69%)

(b) Presented with meta-analysis.

According to the above results, it is only two parameters that can be statistically combined in meta-analysis on the peripheral and placental parasitaemia.

Table 7: The outcome for peripheral parasitaemia in two trials;

Study	SP group (n/N)	Control group (n/N)	Weight (%)	RR (95%CI)	Protective efficacy in %(95%CI)
1	19/350	134/377	89.2	0.15 (0.10, 0.24)	85% (76%-90%)
2	2/71	12/38	10.8	0.09 (0.02, 0.38)	91%(62%-98%)
M-H pooled RR				0.14 (0.09, 0.22)	86% (88%-91)

Test for heterogeneity chi-square = 0.48, df = 1, p = 0.487
Test for overall effect of RR = 1: z = 8.67, p = 0.000

Figure 2: Relationship between peripheral parasitaemia and SP/SP use in 2 published articles.

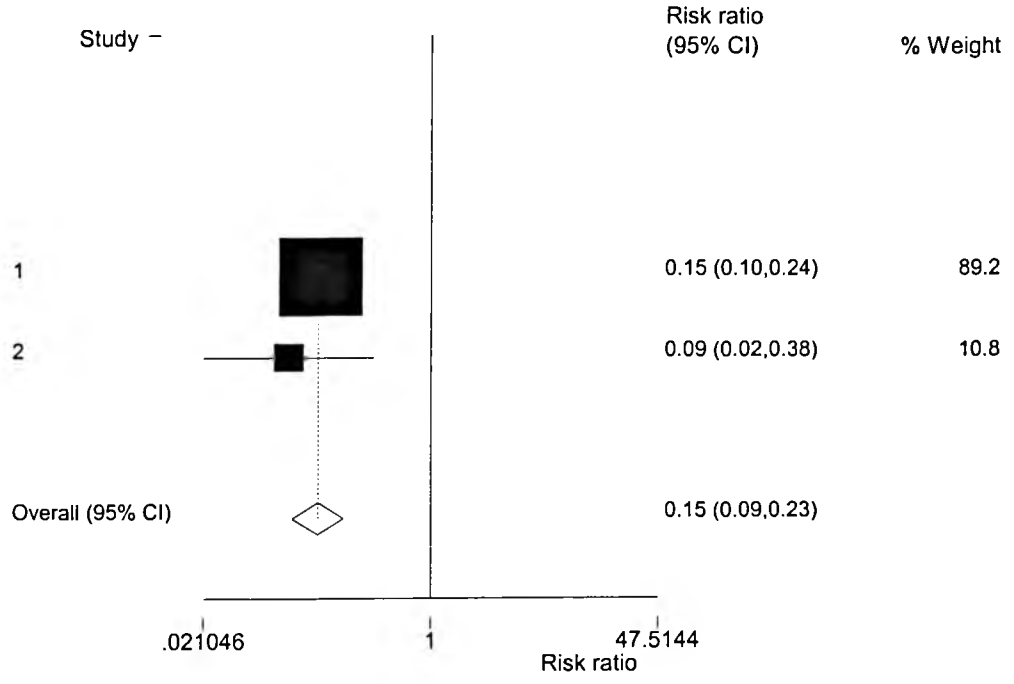
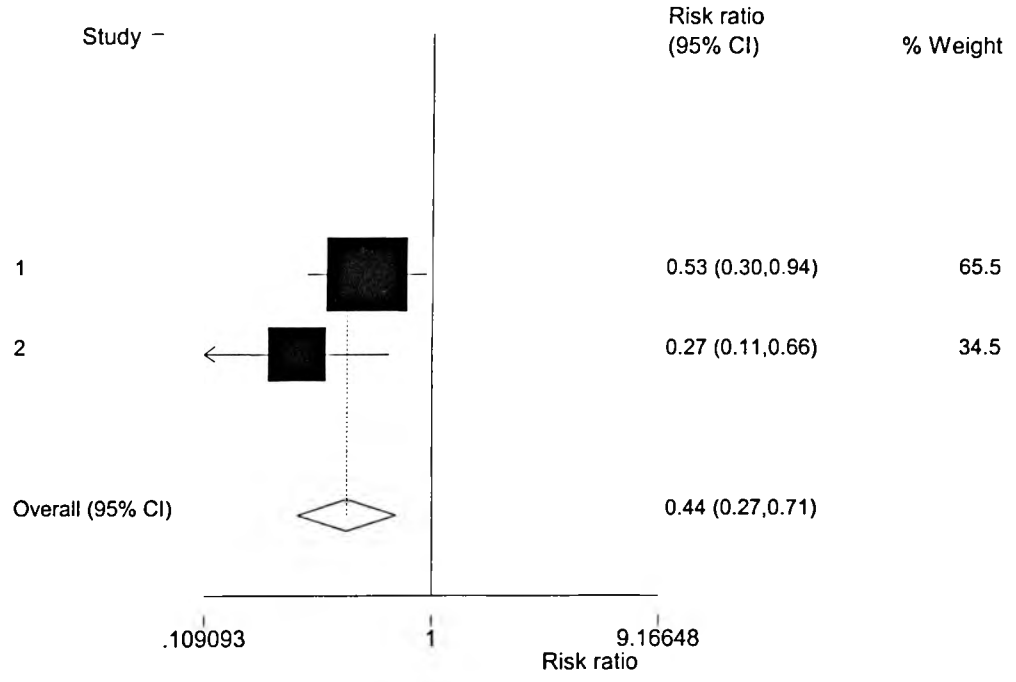


Table 8: The outcome for placental parasitaemia in two trials

Study	SP group (n/N)	Control group (n/N)	Weight (%)	RR (95%CI)	Protective efficacy in %(95%CI)
1	16/205	29/196	65.5	0.53 (0.30, 0.9)	47%(10%,70%)
2	6/71	12/38	34.5	0.27 (0.11, 0.66)	73%(34%,89%)
M-H pooled RR				0.44 (0.27, 0.71)	56% (29%,73%)

Test for heterogeneity chi-square = 1.56, df = 1, p = 0.212
Test for overall effect of RR = 1: z = 3.37, p = 0.001

Figure 3: Relationship between placental parasitaemia and SP/SP use in 2 published articles.



The review found that two studies were homogeneous for combinability in clinically relevance based on test heterogeneity (table 7 and 8). This homogeneous facilitated sensible statistical meta-analysis to be done, since meta-analysis requires combination of at least two studies for producing overall estimate of the treatment effect (42).

The graphical display (Fig 2 and 3) has the vertical line drawn at relative ratio of one (unity) represents 'no effect' and confidence interval overlapping this line represents the lack of a statistically significant effect. Therefore the both displays indicate the degree of decreasing peripheral and placental parasitaemia at significant levels since the overall confidence intervals do not overlapping lines, that is, statistically significant. Therefore, based on these

studies, the efficacy of SP/SP against chloroquine on peripheral parasitaemia, placental parasitaemia, severe anaemia a LBW outcomes and whether intermittent SP/SP has adverse side effect or not was assessed.

4.0 DISCUSSION:

This quantitative systematic review evaluated the results of two papers on the efficacy of double dose sulfadoxine-pyrimethamine (SP/SP) treatment during pregnancy.

In combining data from two trials (study 1 and 2) gives the efficacy of 86% (95% CI 78% to 91%) among the pregnant women got SP/SP during pregnancy against malaria peripheral infection with risk ratio (RR) of 0.14 (95% CI 0.09, 0.22), Table 7. This implies that SP/SP decreases the burden of peripheral parasitaemia compared to chloroquine/placebo, Fig 2. In supporting the outcome measure, it has been noted that SP/SP results in significantly reduced of peripheral malarial infection in primigravidae and multigravidae when compared to chloroquine (43).

Combining data from 2 studies resulted in a risk ratio of 0.44 for pregnant women who received SP/SP (95% CI 0.27 to 0.71), which is equivalent to protective efficacy of 56% (95% CI 29% to 73%) against malaria placental infection, Table 7. It means that SP/SP can reduce placental parasitaemia compared to chloroquine, Fig 3. In other words, SP/SP reduced the prevalence of placental parasitaemia at delivery by 56%. In addition to that it has been reported that SP/SP reduced placental infection among pregnant women compared to single dose of SP (44).

Without meta-analysis, study 1 shows that the efficacy of SP/SP on severe anaemia which seemed to be less in comparison with peripheral and placental parasitaemia. Its protective efficacy was 39% with risk ratio of 0.61 (0.45, 0.84) as shown in table 5. It has been reported that two doses of SP might have little effect on severe anaemia at delivery (45). Not only malaria causes anaemia but also poor nutrition as causal factor for anaemia in pregnancy (46). This may be true since the study participants (from study 1 and study 2) came from rural settings where most inhabitants depend on subsistence farming. In order to reduce the risk of anaemia among pregnant mothers in rural setting, it is important to take care of provision of social services based on equity and poverty elevation programmes should implemented in such settings. For instance, poor infrastructures in rural areas like roads, this may limit equal distribution of insecticide treated nets for malaria prevention to be available in their areas, and therefore it would be useful to improve infrastructures in rural areas.

In considering study 2 alone, no protective efficacy was shown by SP/SP on LBW at delivery with comparison to chloroquine, its 95% CI of risk ratio is across one, 0.64 (95% CI 0.31, 1.35), as shown in table 6. The author suggested that extremely large sample sizes are required to detect statistically significant differences in LBW when controlling for the many causative factors for LBW. It should also be born in mind that the prevalence of LBW differs from country to country and is influenced by several factors (47). Other studies not included in the meta-analysis have shown that 2 doses of SP decreased LBW prevalence (44, 45, 48).

A few pregnant women reported adverse reactions of SP/SP (appendix 1 and 2). It was stated that there was no evidence of a teratogenic or otherwise harmful effect of gestational exposure to SP (47). No pregnant mothers refused to take SP in both studies 1 and 2. This implies that there were not

significant side effects that impeded pregnant women from using SP/SP treatment, and therefore this intervention can be recommended for wide scale use with a follow up of rare side effects.

The limitations of this meta-analysis fall into three categories, those attributable to the design of the reviewed studies, those attributable to the data available for analysis and those attributable to the combinability of parameters reported.

Only one study fulfilled the study design criteria set in the quality assessment, Table 1. Since the other study did not meet all the quality criteria, it was difficult to provide a reliable overall estimate for the efficacy of sulfadoxine - pyremethamine in pregnancy.

Given the inclusion criteria, the meta-analysis was limited in coverage with only two countries from Africa included. No suitable studies were found from outside Africa. This may limit the generalisability of the review results to malaria endemic areas in different settings.

Data for meta-analysis were combined on two parameters. These were peripheral and placental malaria infections. Data for severe anaemia and low birth weight outcome couldn't be combined in more than one study. This could reduce lack of meta-analysis based evidence in these two parameters. In addition to that peripheral and placental parasitaemia are

intermediate outcomes in pregnancy compared to severe anaemia and low birth weight outcome. As expected it was ease to demonstrate an impact of the SP intermittent therapy with intermediate outcomes (peripheral and placental parasitaemia) than definitive outcome (low birth weight).

The available evidence from this review was not consistent for the all outcomes. To establish the relative contribution of SP/SP treatment for all outcome measures in this review data from a CQ/CQ control was combined with placebo control and there was no indication in the revel of CQ resistance in the study areas hence the assumption of CQ/CQ = placebo may be wrong. Therefore, Randomised Control Trials should include comparison of the efficacy of CQ with SP as antimalarial treatment in preventing severe anaemia, LBW, peripheral and placental parasitaemia at once.

5.0 Conclusion and recommendations:

Based on a meta-analysis of data from two prospective trials, it is concluded that double dose sulfadoxine-pyrimethamine (SP/SP) is potentially useful for pregnant women in areas where malaria is endemic

More information is required regarding the efficacy and safety of intermittent treatment with SP/SP in different malaria endemic settings.

Therefore, further evidence about the efficacy of SP/SP is required.

APPENDICES

Appendix 1: Study 1:

(**Shulman et al CE**. Intermittent sulfadoxine-pyremethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo-controlled trial. The Lancet.1999 Vol 353)

Study country	Kenya
Study date	January, 1996 to April, 1997
Study design	Randomised placebo-controlled trial
Setting	Study took place in Kilifi, a mainly rural district on the coast of Kenya.
Sample size	Randomised 1264 women.
Lost to follow-up	132 women.
Participants	Women who were attending at Vipingo Health Centre. Women should be in their 1st pregnancy, between **16- and 30- weeks gestation.** The presence of peripheral parasitaemia was main determinant of severe anaemia.
Reported antimalarial regimens	SP/SP or placebo– depended on gestation at recruitment. 3 doses at 16 - 19 weeks of gestation. 2 doses at 20 – 26 weeks of gestation. 1 dose at 27 – 30 weeks of gestation.
Comparison interventions **(Interested in the review)**	SP/SP or placebo; 2 doses at 20 – 26 weeks of gestation.
Outcome measures at delivery for comparison regimens.	**Peripheral parasitaemia;** (Protective efficacy; 85% [76-90%] p< 0.0001) Placebo group 35% (134/377) of women had infection. SP group 5% (19/350) of women had infection. **Placental parasitaemia;** Placebo group 14.8% (29/196) of women had infection. SP/SP group 7.8% (16/205) of women had infection. **Severe anaemia;** (Protective efficacy; 39% [16-55%] p= 0.002) Placebo group 23% (88/378) of women had severe anaemia. SP group 14% (50/350) of women had severe anaemia.
Side effects of SP to women.	4 women in the SP group and 3 women in the placebo group were suspended because of suspected minor drug reaction.
Comments	One and three doses of SP regimen were not interested in our review.

Appendix 2: Study 2:

(**Linda J. Shultz et al**.The efficacy of antimalaria regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental plasmodium falciparum infection among women in Malawi. Am. J. Trop. Med. Hyg, 1994; 51, 5: 515 - 522)

Study country	Malawi
Study date	1st March to 20th October 1992
Study design	Quasi-experimental study
Setting	70 villages with estimated total of population 60,000 in Mangochi districts in southern Malawi
Sample size	Selected 357 women
Lost to follow-up	50 women.
Participants	Women who were attending at antenatal clinics of two rural hospitals. Women should be in their 1st or 2nd pregnancy, between **16- and 32- weeks gestation.**
Reported antimalarial regimens	-CQ/CQ -SP/CQ -SP/SP
Comparison regimens (Interested in the review)	CQ/CQ – an initial treatment dose of CQ at enrolment followed by CQ weekly until delivery. SP/SP – an initial treatment dose of SP with second dose at the beginning of the third trimester.
Outcome measures at delivery for comparison regimens.	**Peripheral parasitaemia; (X^2 – test, p< 0.001)** CQ/CQ group 32% (12/38) of women had infection. SP/SP group 3%(2/71) of women had infection. **Placental parasitaemia; (X^2 – test, p< 0.006)** CQ/CQ group 32% (12/38) of women had infection. SP/SP group 9% (6/71) of women had infection. **LBW outcome; (X^2 – test, p< 0.30)** CQ/CQ group 27% (10/38) of women had LBW babies. SP/SP group 17% (12/71) of women had LBW babies.
Side effects of SP/SP to women.	Few women complain for side effects.
Comments	The study included SP/CQ treatment regimen that was not interested in the review.

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