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The effectiveness of intermittent preventive therapy with sulphadoxine and pyrimethamine on the risk of low birthweight in West Africa: a systematic review and metal-analysis

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THE EFFECTIVENESS OF INTERMITTENT PREVENTIVE THERAPY WITH SULPHADOXINE AND PYRIMETHAMINE ON THE RISK OF LOW BIRTHWEIGHT IN WEST AFRICA:

A SYSTEMATIC REVIEW AND META-ANALYSIS

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A Research report submitted to the Faculty of Health Sciences in partial fulfillment of the requirements for the Degree of

MASTER OF SCIENCE IN EPIDEMIOLOGY AND BIOSTATISTICS

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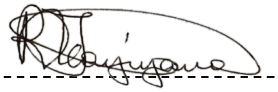
Declaration

I, Emmanuel Oloche Otukpa, student number 753575, declare that this research report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Research report. It is being submitted in partial fulfilment of the requirements for the Degree of Master of Science in Epidemiology and Biostatistics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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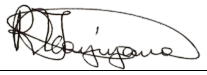
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Signature of Primary Supervisor:  Date: 8th August 2018

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of his research report.

Title: **The effectiveness of intermittent preventive therapy with Sulphadoxine and Pyrimethamine on the risk of low Birthweight in West Africa:**

A systematic review and meta-analysis

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1st author	Emmanuel O. Otukpa		08/08/2018
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Dedication

I dedicate this research to my parents Mr. Joseph Audu Otukpa and Mrs. Priscilla Otukpa for their continuous support and encouragement.

Abstract

Background

Intermittent preventive therapy with Sulphadoxine-Pyrimethamine, used in the prevention of malaria in pregnancy is the standard used in over 37 countries in Sub-Saharan Africa. With an increasing burden of malaria in pregnancy as well as the increased potential for *P. falciparum* resistance and inadequate dosage regimentation, there may be a reason to believe IPTP-SP may no longer be effective for the prevention of malaria in pregnancy, in endemic regions of the continent specifically in West Africa.

Methods

A stepwise, systematic and extensive literature of online databases was performed based on predefined search terms. The Malaria in pregnancy library, PubMed, and Google Scholar were searched for randomized control trials conducted within the years of 2000 to 2017, which compared Intermittent preventive therapy with Sulphadoxine and Pyrimethamine with other prophylactic drug interventions, in the West African sub-region was done. Eligible studies included randomized control trials of published or unpublished original research studies.

Results

Of 60 studies, 10 trials with 15,936 pregnancies were included in the final meta-analysis. Pregnant women in the Intermittent preventive therapy with Sulphadoxine and Pyrimethamine groups showed no significant difference in risks of having low birthweight infants from groups that used other interventions (RR = 0.94; 95% CI [0.78 – 1.13], I^2=77) showing that IPTP-SP use did not inherently reduce the risk of pregnant women having low birth weight babies. The outcome of low birthweight at term in the IPTP-SP groups was 930 events out of a total population of 7131. Other outcomes showed the same consistency.

Conclusion

Among pregnant women in West Africa Intermittent Preventive Therapy with two or more doses of Sulphadoxine and Pyrimethamine did not inherently reduce the risk of adverse birth outcomes from malaria in pregnancy. The main objective of this analysis was to evaluate the effectiveness of two or more dose of IPTP-SP in preventing adverse birth outcomes, in the context of public health, the evidence shows that this effectiveness is not upheld in a malaria endemic region.

Keywords

Malaria in Pregnancy, Low Birthweight, Adverse birth outcomes, IPTP-SP, West Africa

Acknowledgment

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List of Abbreviations

MIP: Malaria in pregnancy;

IPTP-SP: Intermittent preventive therapy with Sulphadoxine and Pyrimethamine;

SP: Sulphadoxine and Pyrimethamine;

LBW: Low Birth Weight;

RBM: Roll back Malaria;

SSA: Sub-Saharan Africa;

ANC: Antenatal care;

FANC: Focused Antenatal care;

PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-analysis protocol;

MDA: Mass Drug Administration;

CQ: Chloroquine;

AL: Artemether-Lumefantrine;

ASAQ: Artesunate and Amodiaquine;

IST: Intermittent Screening and Testing;

MQ: Melfoquine;

AQ: Amodiaquine

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Introduction

In sub-Saharan Africa, thirty countries account for 90% of all deaths attributed to malaria globally [1]. In West and Central Africa, the combined burden of malaria in the Democratic Republic of Congo and Nigeria accounted for more than 40% of all deaths attributed to malaria [2]. Recent studies in the region have also shown the propensity of SP resistance, by *P. falciparum* malaria; as characterized by the presence of molecular biomarkers of resistance on the parasite [3].

Every year, roughly 25 million African women who reside in malaria-endemic areas become pregnant and therefore become at risk of *P. falciparum* malaria infection during their pregnancy [4]. Malaria in pregnancy (MIP) is capable of bringing about adverse effects on the unborn fetus and the mother; producing maternal anemia, fetal loss, premature delivery and, intra-uterine growth delay through the impairment of fetal nutrition. It is commonly what leads to births of infants with Low Birthweight (LBW), which is a risk factor for neonatal mortality[4]–[6]

Intermittent preventive therapy of malaria in pregnancy (IPTP) as recommended by the world health organization (WHO), is essentially the administration of a single dose of the Sulphadoxine/Pyrimethamine (SP) combination anti-malarial medication at least twice during pregnancy regardless of the status of current infection [7].

In endemic regions, MIP may constitute up to 5 – 14% of underweight births and 30% of avoidable LBWs as well as 15% of anemia during pregnancy [8]. When considering all year round transmission and the potential for resistance, the standard 2 dose IPTP-SP regimen may be inadequate in providing protection in the time period of 4-10 weeks of pregnancy which is a critical period for fetal weight gain [9]. Therefore, the implementation of the WHO policy of IPTP-SP continues to face challenges, such as the timing of SP administration [10], traditional practices of the regional population [11],[12] and the increasing rate of SP resistance in the general population [13].

The resistance to SP has been observed worldwide and is as a result of point mutations that

accumulate at multiple sites in genes within *P.falciparum*, increasing its tolerance to the drug in vitro [14].

The rationale for conducting this research stems from the fact that West Africa is a malaria endemic zone in SSA with all year round transmission [15]. Therefore, it is possible that despite a certain degree of immunity to malaria in the general population; MIP in same population continues to pose a public health risk in maternal and child health.

We conducted a systematic review and meta-analysis of trials to determine whether IPTP-SP containing two or more dose regimens remains effective in the prevention of adverse birth outcomes such as LBW, parasitemia, and maternal anemia amongst others, in pregnant women residing in West Africa.

Materials/Methods

Protocol and registration

The protocol for this systematic review and meta-analysis is based on the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The protocol for this systematic review and meta-analysis has not been registered with PROSPERO and is made available on request.

Eligibility Criteria

The inclusion criteria, as well as the outcomes and methods for the analysis, is specified in the protocol a summary is presented below;

Inclusion criteria

This systematic review included;

1. Published and/or unpublished original research studies
2. Randomized or quasi-randomized controlled trials carried out in West Africa with pregnant women as participants
3. Research studies published either in French and/or English
4. Research studies published between 2005 and 2015

5. Conducted in any and all parts of West Africa

Exclusion criteria
This systematic review excluded;

1. Research studies that includes other prophylactic anti-malarial agents
2. Studies that are not in line with the WHO roll back malaria policies
3. Research studies the focus on the beneficial effects of folic acid
4. Research studies that looked at the treatment of MIP rather than the prevention
5. Studies, where participants were on clinical treatment or studies including mass drug administration (MDAs) were excluded.

The inclusion of trials was also not restricted by gravid and HIV status

Comparator
This systematic review and meta-analysis compares populations which incidences of the primary and secondary outcomes of interest did not occur in but took part in the aforementioned RCT studies as participants; and populations to which incidences of the primary and/or secondary outcomes were documented in the same studies. The studies were randomized controlled trials conducted with pregnant women as participants, who reside in West Africa comparing the standard dosage regimen with SP with any other intervention.

Outcomes
The primary outcome measure is LBW. This outcome is defined as the weight of a live birth less than 2500g (2.5kg) [16]. Secondary outcomes include; parasitemia as defined as the presence of the malaria parasite through microscopy confirmation, and anemia; where anemia was defined by gauged maternal hemoglobin levels less than 11 g/dl as low, and for levels 6 – 8 g/dl for moderate to severe anemia. For the purposes of this review, the term *effectiveness* refers to the degree to which IPTP-SP is successful in preventing MIP and subsequent adverse birth outcomes. The studies included in this systematic review and meta-analysis used studies that specified the intention to treat (ITT) analysis in their data analysis.

Information sources and search strategy

The PICO (Patient, Intervention, comparator and outcome) framework was used to identify applicable terminology for the review as inclusion in the search strategy [17]. The combination of keywords relating principally to the intervention comprised the search terms. A stepwise, systematic and extensive literature search of online databases was performed based on the identified search terms. The search strategy included MIP online library as well as PubMed and google scholar. The reference list of all studies and articles identified was also checked. Refer to Appendix A for details and outputs of the database search

Study selection

Two independent researchers screened the titles and abstracts of the search results for potentially relevant studies. The two researchers then reviewed the full reports of all retrieved studies and independently assessed eligibility using a specially designed form based on the inclusion and exclusion criteria. The author assessed all foreign language papers for eligibility and excluded studies and their reasons for exclusion were reported (a summary of the selection is shown in Figure 1).

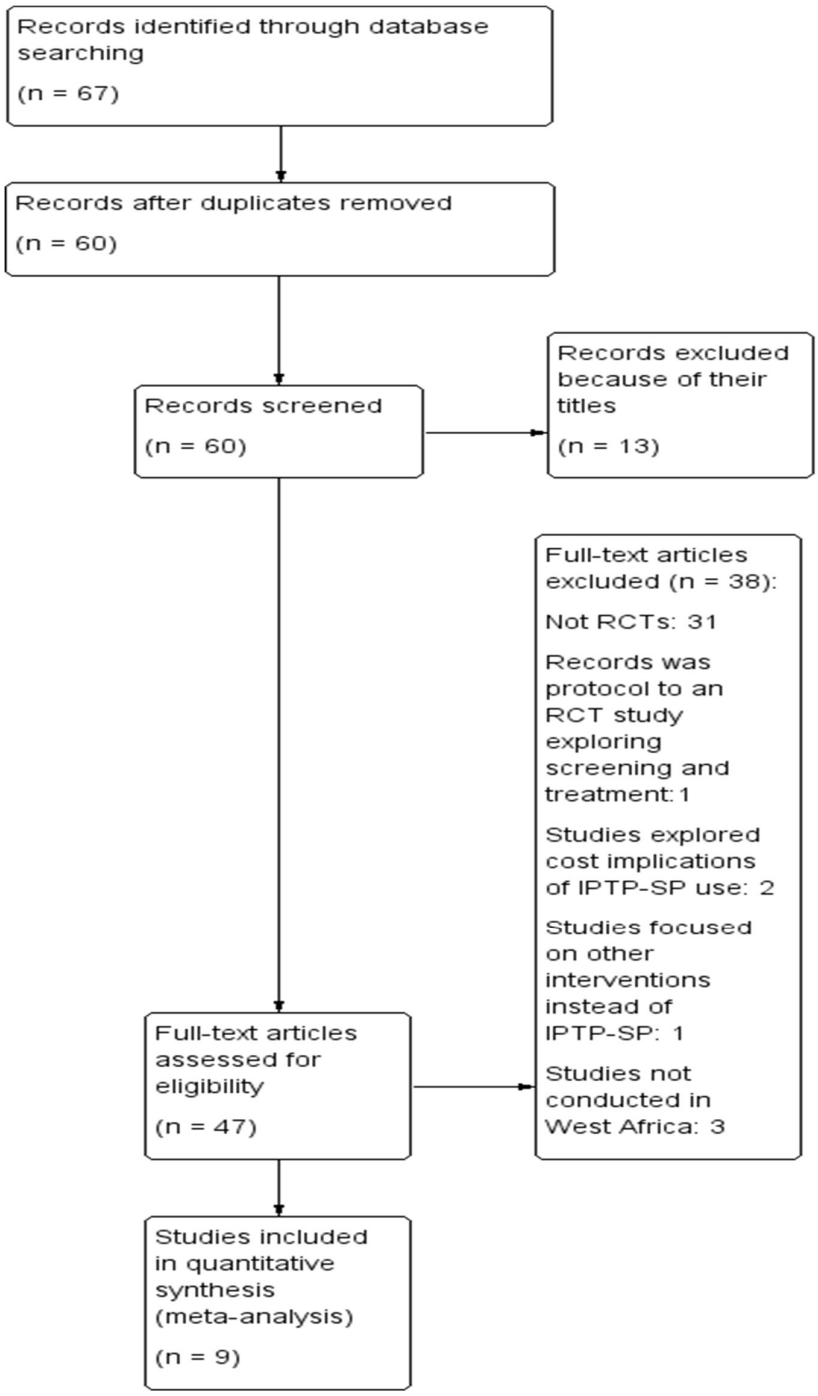


Figure 1 Study flow diagram

Data extraction

We conducted data extraction using a specially designed standardized data extraction form that collected information on the basic characteristics concerning regimen and coverage, duration of follow-up, and outcomes.

Data synthesis and statistical analysis

The meta-analysis of data on the effectiveness of the IPTP-SP interventions was conducted using Review Manager Version 5.3.5 (Cochrane Collaboration Software) where summary Risk ratios (RRs) of observing adverse effects were calculated using random effects model. I^2 and 95% confidence intervals were used to quantify heterogeneity. Results that show heterogeneity between 25 and 50% were indicative of moderate heterogeneity, from 50 – 75% showed substantial heterogeneity and above 75% will be of significant heterogeneity. The findings of this review were reported in conformity with the PRISMA guidelines [18].

A simple sensitivity analysis was done to gauge the extent of the weight certain studies had on the overall analysis for certain outcomes. The process involved the repetition of the primary analysis with an altered study dataset i.e. removal of some included studies. The choice of study to remove was based on the quality and sudy size, the sensitivity analysis did not involve an alteration to the statistical model employed in the analysis.

Risk of bias in individual studies

The assessment of bias within individual studies in this quantitative meta-analysis follows the taxonomy suggested by Higgins et al. in the Cochrane Handbook as a common comprehensive well-disseminated approach of bias assessment. This systematic review and quantitative meta-analysis used the Cochrane public health reviews Groups' recommended Effective public health practice quality assessment tool for all quantitative studies [19]. The tool guided the selection of studies towards adequate representation of samples as they relate to the comparison of baseline groups, the quality of data collection and the rate at which participants leave the study without duly been observed for the primary outcome of interest. The tool for assessing the risk of bias was used to determine the quality of the included studies as low (high risk of bias) and high (low risk of bias) or not applicable. During the course of the review, the two reviewers came to an agreement on which classification a study falls under. When views differed, in some cases a third reviewer was consulted as needed.

Results

Study selection

We conducted the initial search in April 2017, and repeated the search in June 2018. In total, we identified sixty-seven records through the database searches; we removed seven records as duplicates. We screened sixty records, from which we excluded 13 because of their titles and abstracts. Forty seven full text articles were then assessed for eligibility, from which 38 were screened out for various reasons (see Figure 1) and finally nine unique studies were included in the final quantitative Meta-analysis (see Table 1). One of the studies [20] included more than one comparison (SP vs. CQ) which subsequently was included as two separate studies.

From the identified studies, 38 studies were excluded because they did not fall in line with the review's inclusion criteria; three studies were not conducted in West Africa; two studies explored the economic cost of prophylactic treatment of MIP; one study was a protocol for an RCT; one study saw the participants have a pre-existing condition i.e. sickle cell anemia; One study was a commentary on IPTP-SP and one study did not directly answer the review question; one study concerned itself with diagnostic testing only and 4 studies had outcomes that were not in line with that of the review.

Study Characteristics

Table 1 Summarizes the number of included RCTs, and the relevant parameters for each study. Most of the studies aimed to investigate the effectiveness of IPTP-SP in comparison with other malaria prophylactic treatment in pregnancy. Among the 9 trials, two of them were open label trials [21][22] while just one was a placebo controlled closed label trial [23]. These included trials were published between 2000 and 2017 and in line with the inclusion criteria; their research spans only countries in West Africa.

Table 1 Characteristics of included trials

Author/Year	Country	Study years	Control Regimen	Intervention Regimen	2nd intervention regimen	Open Label/Placebo-controlled	Lost to follow up, No (%)
Briand et al. 2008	The Republic of Benin	2004 - 2005	2 dose	3 dose		n/a	n/a
Briand, 2009	The Republic of Benin	2005 - 2008	2 dose	2 dose		**Open Label**	71(4%)
Clerk et al. 2008	Ghana	2004 - 2007	1 dose (54%) 2 dose (36%) 3 dose (11%)	1 dose		Closed label	
Gies et al. 2009	Burkina Faso	2004 - 2006	>3 dose	2 dose		Closed label	577(20%)
Maiga et al., 2011	Mali	2006 - 2008	2 dose	3 dose		Closed label	639(7%)
Mbaye et al., 2006	The Gambia	2002 – 2004	>3 dose	> 3 dose		Closed label/placebo controlled	459(1.7%)
Tagbor et al. 2010	Ghana	2007-2008	3 dose	3 dose	3 dose	Open label	14(0.4%)
Tagbor et al. 2015	The Gambia, Mali, Burkina Faso, Ghana	2010 - 2011	3 dose	3 dose		Closed label	592(11%)
Tiono et al. 2009	Burkina Faso	2005	3 dose	3 dose	3 dose	Closed label	n/a

Risk of Bias within studies

For this quantitative meta-analysis, we used the Cochrane public health reviews Groups' recommended Effective public health practice quality assessment tool for all quantitative studies to assess risk of bias.

The risk of bias assessment is outlined in Figure 2. In all studies, except for the Briand 2008 study not all participants and personnel were blinded to the intervention. A few studies had incomplete outcomes and selective reporting. An attempt to contact two authors for clarification concerning blinding of participants and personnel to the outcomes of interest proved abortive.



Figure 2 Risk of Bias Asses reviews authors judgement about each risk of bias item presented as a percentage for all included studies

Primary outcome: Low Birthweight

The results here shows that the use of IPTP-SP is more effective in curtailing LBW. Women in the IPTP-SP group had fewer infants with LBW however There is little or no difference in the risk of pregnant women having LBW infants whether IPTP-SP was used or not (RR = 0.94; 95% CI [0.78 – 1.13], I^2=77%) (Figure 3). Nine hundred and thirty (930) events were observed out of 7131 participants in the IPTP-SP arm whilst other intervention had 1184 events out of 8605 participants all from 10 trials. Trials that have the widest confidence intervals [24]–[26] have the smallest study population size, and trials with the more narrow confidence intervals have the largest weight [22], [20], and [27] at 13.0%, 11.4%, and 10.3% respectively. The trial with the largest effect estimate [26](RR 2.02 95% CI [1.27 – 3.20]) (Figure 3) carries a 7.4% weighting favoring other MIP interventions. Overall heterogeneity is substantial and statistically significant. Sensitivity analysis shows that after the removal of three studies with questionable qualities, the point estimates for LBW were (RR 0.97 95% CI [0.85 – 1.11], I^2 = 47%) (Figure 8; Appendix A) bringing the risk closer to favoring other interventions with a reduced heterogeneity. Further removal of any individual trial had relatively little effect and the pooled results did not show statistical significance at P = 0.68 with the random-effects model (Figure 8).

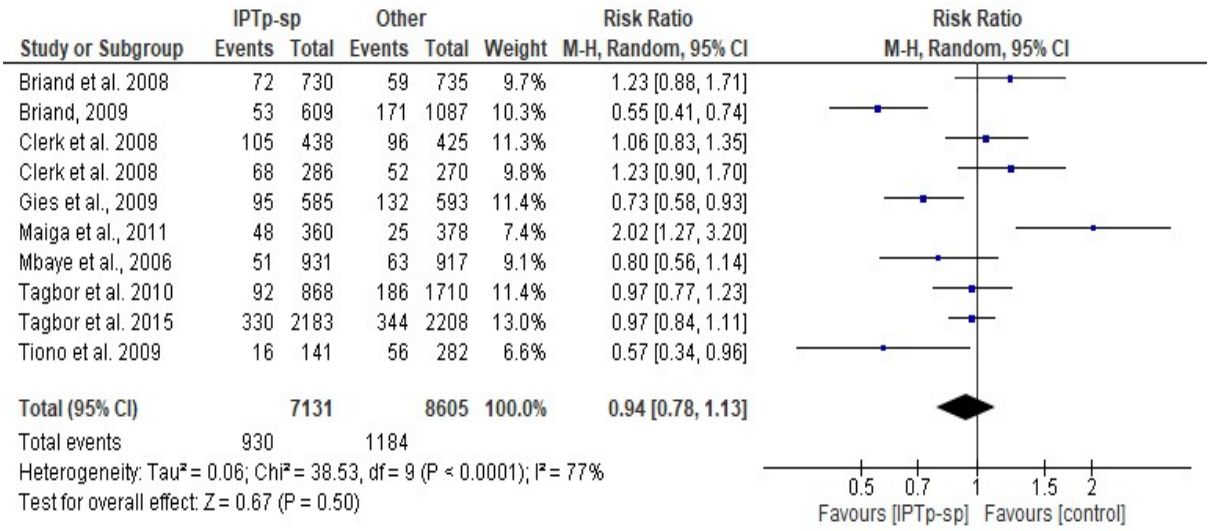


Figure 3 Meta-analysis of the Risk of Adverse Birth Outcomes: Low Birthweight (LBW)

Secondary outcomes

Maternal Parasitemia

The results for this outcome show that Two hundred and sixty five (265) events were observed in the IPTP-SP group out of a total 3231 participants as compared to 476 events out of 3640 in the other interventions group all from a total of five trials that explored the association between and IPTP-SP and maternal parasitemia The risk of having maternal parasitemia (malarial infections at term) was slightly lower when IPTP-SP is used as compared to when other interventions were used (RR 0.68: 95% CI [0.45 – 1.04], I^2 = 87%) (Figure 2). The analysis shows substantial heterogeneity. A sensitivity analysis done for this outcome isolates one study as having a strong effect on the analysis [20]. On removal of the study the effect estimate changes (RR 0.56: 95% CI [0.39 – 0.81] I2 = 84%) reducing heterogeneity to 84%.

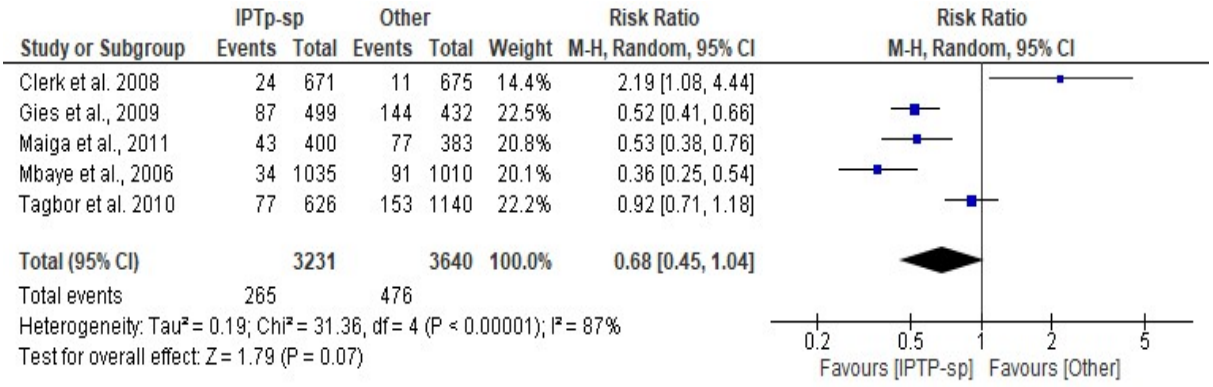


Figure 4 Meta-analysis of the Risk of maternal parasitemia

Maternal Anemia

The outcome of interest here was divided into 2 subgroups for the participants that experienced severe anemia and for the participants who experienced regular anemia.

- Anemia 8 – 11g/dl: this subgroup showed that pregnant women in the IPTP-SP group had higher incidences of maternal anemia as compared to other interventions (RR 1.02; 95% CI [0.92 – 1.13], I^2 =67%) (Figure 4). One thousand two hundred and eighty nine (1289) events were observed in the IPTP-SP group out of a total of 3080 participants as compared to 1221 events out of 2985 participants observed in the other intervention

groups. Generally, the average weighting was within 10%. Two trials constitute the highest effect measure [22],[26].Heterogeneity was substantial at 67% and statistically significant (Figure 5).

- Severe anemia <7g/dl: This subgroup shows that pregnant women in the IPTP-SP group had a lower incidence of severe maternal malaria at term (RR 0.93; 95% CI [0.68 – 1.29], I^2=36%). Only one study completely crossed the line of no effect [20] (RR 2.49; 95% CI [1.05 – 5.92]) (Figure 5).

The overall heterogeneity was at 57% with effect estimate (RR 0.97; 95% CI [0.58 -1.11]) statistically significant. The analysis of the outcome of spontaneous abortion and neonatal death is shown in figures 6 and 7 respectively (see Appendix B). Table 2 shows the summary of the analysis.

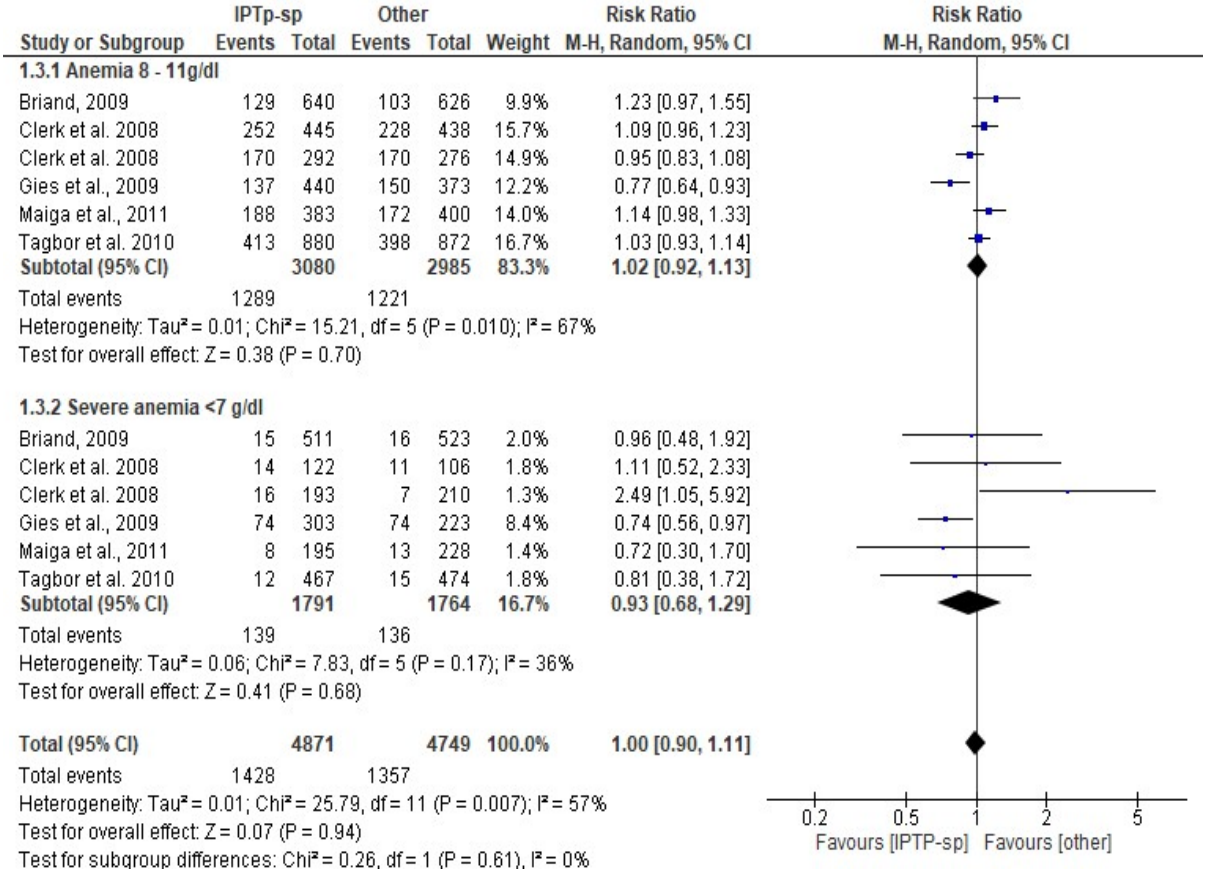


Figure 5 Meta-analysis of the Risk of Adverse Birth Outcomes: Maternal anemia

Table 2 Summary of the Random-effects Meta-analysis of trials

		IPTP-SP		Other Interventions		Random-Effects Model		
Outcome	**Number of studies**	**Number of events**	**Total Number**	**Number of studies**	**Numbe r of events**	**MH Risk ratio (95% CI)**	**P-value**	**I^2**
Low Birthweight	10	930	7173	1184	8605	0.94 [0.78, 1.13]	0.50	77%
Maternal Parasitaemia	5	265	3231	476	3640	0.68[0.45, 1.04]	0.07	87%
Maternal Anemia		1289	3080	1221	2985	1.02[0.92, 1.13]	0.70	67%
Anemia 8 – 11 g/dl								
Severe Anemia <7 g/dl		139	1791	136	1764	0.93[0.68, 1.29]	0.68	36%
Total	6	1428	4871	1357	4749	1.00[0.90, 1.11]	0.61	57%
Spontaneous Abortion	7	80	6522	90	7625	0.95[0.70, 1.13]	0.78	0%
Neonatal Death	7	184	6516	249	7581	0.91[0.66, 1.26]	0.58	56%

Discussion

Summary of evidence

It was the intention of this quantitative meta-analysis to explore whether IPTP-SP remains effective in preventing adverse birth outcomes because of MIP in endemic regions. The results show that IPTP-SP shows no substantial effective risk reduction in preventing adverse birth outcomes as a result of MIP in West Africa. Conversely IPTP-SP remains the choice prophylactic treatment agent due to its relative efficacy and safety. This meta-analysis of 9 trials demonstrated that two or more dose regimens of IPTP-SP did not show substantial potency in preventing MIP outcomes although are associated with less parasitemia at term only. LBW, maternal anemia, neonatal death, and spontaneous abortion showed not statistically significant difference in risk whether IPTP-SP was used or not.

The pooled analysis of the outcome of maternal parasitemia at term was favorable to IPTP-SP with overall risk of incidence at 0.46 as compared to other interventions. These results included five studies that showed a substantial heterogeneity of 87% and was of statistical significance.

No one single study took the bulk of the weighting. The degree of association observed was noticeable as at least four of the five trials in the meta-analysis, pregnant women were issued ITNs and it is therefore assumed that they were protected from the vector of transmission.

Concerning LBW, the meta-analysis showed an overall and marginal risk of incidence of LBW at 0.93, with 9 trials cutting across 17 years. With a moderate heterogeneity of 74%; showing no statistical significance. The association with this outcome was relatively consistent across the trials and there was no suggestion that the results were affected by the weight of one influential trial.

We subjected the outcome of maternal anemia to subgroup analysis. The result favors the use of IPTP-SP especially in severe maternal anemia at term. For anemia that ranged from 8 – 11 g/dl, the overall effect estimate was 1.00, which means there was no difference between the effect of IPTP-SP and other interventions when it comes to preventing anemia because of MIP. In a similar vein, when it comes to severe anemia, the effect measure was 0.87, which emphasizes IPTP-SP slightly protective effect; there was a reduced heterogeneity of 30%. With an effect estimate of 0.97 risks of incidence, the effectiveness of IPTP-SP in relation to maternal anemia is somewhat deceiving as aside from malaria infection anemia could be because of other factors, which will be looked at in coming sections.

The outcome of spontaneous abortion was similar to maternal anemia. One study, however, consumed a larger percentage of the weighting [28] taking 47.1% of the total weighting. This trial favors other interventions with a significantly small confidence interval. All the seven trials here showed overlapping confidence intervals which all included unity, providing, an overall effect estimate of 0.95; with 0% heterogeneity. When it came to the outcome of neonatal death, the overall effect measure of 0.90 favored the use of IPTP-SP without statistical significance. As less pregnant women experienced the neonatal death of their infants, the analysis showed

moderate heterogeneity of 60% and the highest weighted study [29] had the smallest confidence interval.

Accounting for heterogeneity

This quantitative meta-analysis aimed to compare and combine estimates of effect across all the included studies. To increase its clinical and public health relevance we try to explore the potential reasons to which the analysis experienced substantial heterogeneity. Statistical heterogeneity comes into play when the true effects being evaluated differ between studies and is detectable when the variation between the results of the studies is above that expected randomly.

For this systematic review and quantitative meta-analysis, it is entirely possible to link the cases of heterogeneity to potential cases of bias illustrated by the bias assessment in Figure 2. For the primary outcome of LBW as shown by the analysis in figure 3. A simple sensitivity analysis isolated 3 studies as being implicated it causing substantial heterogeneity [22][26][25] an analysis without the three studies is shown in appendix B reducing the overall heterogeneity to 47% (Figure 7). Aspects of those three trials can explain the substantial heterogeneity seen in figure 3. The Briand 2009 study is an open label equivalence trial comparing SP with MQ as a standard 2-dose regimen as such participants and personnel were not blinded to the intervention and/or outcome. A major contribution to bias is the fact that randomization was done according to gravidity and maternity clinic.

The other 2 studies; Tiono et al 2009 and Maiga et al 2011 have one thing in common; the heterogeneity comes from the fact that the structure of the trial was fundamentally unique. Tiono et al 2009 compared three preventive treatment regimens involving CQ, SP and a composite group referred to as Classical Weekly Chemoprophylaxis using CQ (CWC). Whilst the Maiga et al 2011 trial just compared the superiority of 3-dose over 2-dose IPTP-SP regimens.

The heterogeneity for the outcome of maternal parasitemia at term comes from the Clerk et al. 2009 and the Tagbor et al. 2010 as exemplified in the analysis (see Figure 8: Appendix A). The heterogeneity in the sensitivity analysis is reduced to 30% without the aforementioned studies. The Clerk study is of significance as it represents one study that is unique in that one of its experimental arms combined SP and AQ. Although study participants and personnel were blinded to the intervention and outcomes, it makes use of SP in two of its experimental arms, in the context of the maternal parasitemia at term; the results are likely to confound the analysis of this quantitative meta-analysis.

Completeness and applicability of evidence

The main objective of this review was to quantitatively determine whether IPTP-SP continues to be a viable agent in the prevention of MIP and its associated adverse outcomes. This is because Malaria still remains a public health threat in the West African sub-region [4]. Due to all year round high transmission rates [30]. It is imperative to note that despite concerted efforts, the high prevalence of MIP in West Africa is most likely due to a combination of the level of effectiveness of IPTP-SP as well as the limited coverage and uptake of IPTP-SP in the region and the rise in IPTP-SP resistance.

Kayentao in 2014 highlighted in an observational study that the use of multiple doses of IPTP-SP was associated with a reduction in the number of LBW babies. He, however, observed that other outcomes such as maternal anemia as well as parasitemia were highly dependent of gravidity [31]. His findings were limited to five districts in Mali. Multiple factors can also come into play when considering the other outcomes i.e. spontaneous miscarriage and neonatal death. In concert with the endemic status of the West African region, factors such as nutrition in pregnancy, species of malaria parasite, growing cases of IPTP-SP resistance, as well as cultural factors ultimately play a role in the proliferation of the explored adverse outcomes of MIP even with the consistent use of IPTP-SP. These are discussed in the limitations sections.

Other reviews have concentrated on the broader regions of SSA; a 2012 review by De Silva explored the malaria transmissibility in urban areas and not on preventive countermeasures of MIP[32]. Conversely, a review conducted by Hill in 2013 looked at the factors which affect the delivery and uptake of interventions geared towards the prevention of MIP. In the context of this review, the hill study explored why interventions such as the use of ITN and IPTP-SP were experiencing seemingly low uptake across SSA. That review concluded that the delivery of IPTP-SP experiences numerous obstacles when it comes to delivery and the overall health system[33], highlighting other factors which include but are not limited to socioeconomic context amongst others. In a way, that study[33] provided a beacon for this review seeing as the included trials took directly to rural areas. Despite the obstacles in IPTP-SP delivery, the results of this review show that its effectiveness is questionable.

In 2013, Kayentao conducted a systematic review and meta-analysis that studies the effectiveness of IPTP-SP using the dosing regimen as a comparator. He found that administration of 3 doses IPTP-SP was more effective than the standard 2 dose regimen [34]. The aforementioned review best agrees with this review, again still looking at the general SSA region where it found a decreased incidence of MIP adverse effects with a higher dosing of IPTP-SP.

Differences between protocol and review

The review protocol intended to use the covariate of average birth weight. This was no longer relevant to the aims of this review. The original protocol intended to look only at trials that provided the 2-dose IPTP-SP regimen. When performing the systematic search, we found out that IPT-SP trials conducted in Africa often implemented greater than 2-dose IPTP-SP regimen. This was because evidence has shown that SP could be used after quickening and therefore implemented as policy. To that effect, this review included trials with greater than 2 dose regimen.

Limitations of the review

This systematic review and meta-analysis is not devoid of limitations. Firstly, although most trials included in the review followed the counterfactual model for causality, any of the adverse outcomes of MIP may not follow such model and it is possible that participants can experience such outcomes without necessarily becoming infected with the parasite. Secondly, this review suspected that the adverse outcomes of MIP are most likely due in part to the possibility of resistance in the parasite through the mutations of the 51, 59 and 108 Pfdhfr genes to IPTP-SP. The review did not focus on areas where these mutations are prevalent as reported in parts of East Africa, which include Rwanda, Uganda and Northern Tanzania. This review also did not factor concomitant use of associated interventions like ITN use and residual spraying. This review does not take into account;

Nutrition in Pregnancy

Regional dietary patterns in concordance with drug administration and uptake are noteworthy in considering adverse outcomes of MIP. Even with proper and adequate dosing of IPTP-SP, inadequate nutrition can help explain outcomes such as LBW and maternal anemia. It is generally known that drug-food interaction may result either in delayed or boosted systemic bioavailability [35]. The results of this review are not explicit in the dietary condition of its participants; it can be assumed that the rural setting of most of the included trials as well as oral dosing style of IPTP-SP may be a contributing factor to the level of effectiveness of IPTP-SP.

Regional traditional practices

The results of this review have shown substantial heterogeneity across the board. This tells us that the study population from each trial in the region carries variations that can be isolated. The traditional practices of the region are shown in a cross-sectional study conducted by Essé, Clémence in 2008. The study discussed the finding that traditional healers preached the avoidance of some food items as a prevention strategy, exclaiming that there was seemingly no consensus on perceived causes and the chosen treatment. Regardless of the reasons (some of which were mystical), more than 50% of the studied population used traditional means of

treatment and prevention whilst a third of the studied population combine Western treatments as well as traditional ones [36].

Conclusion and recommendations

The cumulative meta-analysis has shown that between 2000 and 2017, the standard 2 or 3-dose or monthly IPTP-SP, showed effectiveness in decreasing the incidence of adverse LBW, maternal parasitemia at term as well as maternal anemia to some degree but statistically was not associated with a decreased risk of LBW and maternal parasitemia than other MIP drug interventions. None of the outcomes has a statistically significant result supporting the use of IPTP-SP despite all year round transmission levels of *P. falciparum* amongst pregnant women in West Africa. To that effect, further research needs to be done into the possible causes why IPTP-SP is not optimal. Although IPTP-SP has been found to be the safe during pregnancy, it is important to investigate other interventions as effective substitutes as well as research closely into the possible rise of IPTP-SP resistance.

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Appendices

Appendix A: Additional Tables

- Table A Database output from search strategy

Database	Search strategy	Date range	Language	Output(Records returned)
Google Scholar	#3 AND #7	2000 - 2017	English	484
Google Scholar	#3 AND #7 AND #10	2000 - 2017	English	456
Google Scholar	#3 AND #7 AND #10 AND #18	2000 - 2017	English	375
Google Scholar	#3 AND #7 AND #10 AND #18 AND #25	2000 - 2017	English	51
PubMed	#3 AND #7	2000 - 2017	English	307
PubMed	#3 AND #7 AND #10	2000 - 2017	English	286
PubMed	#3 AND #7 AND #10 AND #18	2000 - 2017	English	192
PubMed	#3 AND #7 AND #10 AND #18 AND #25	2000 - 2017	English	65
MIP library	#3 AND #7	2000 - 2017	English	432
MIP library	#3 AND #7 AND #10	2000 - 2017	English	306
MIP library	#3 AND #7 AND #10 AND #18	2000 - 2017	English	184
MIP library	#3 AND #7 AND #10 AND #18 AND #25	2000 - 2017	English	54

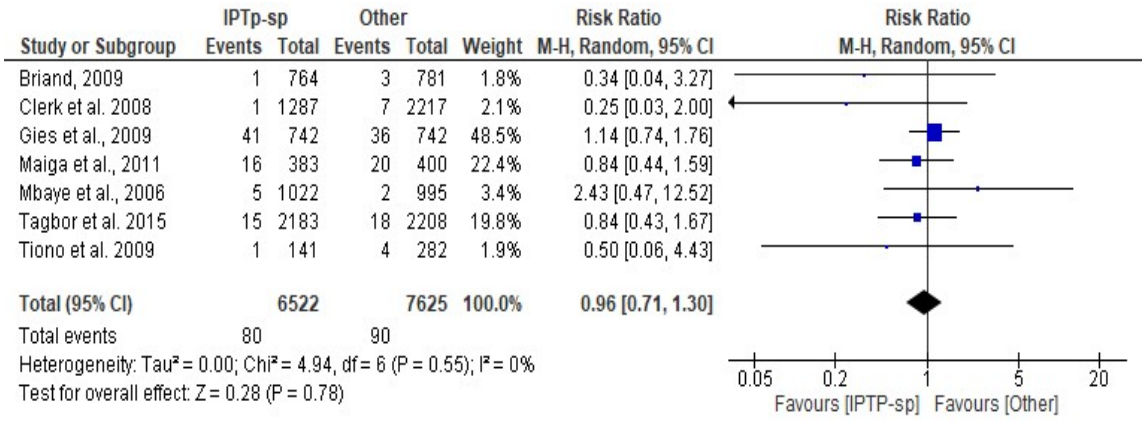
- PRISMA Checklist

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.

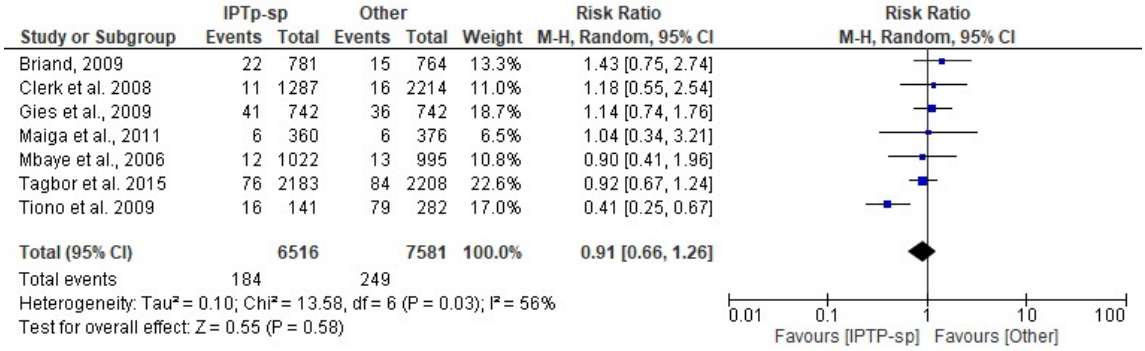
Section/topic	#	Checklist item
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

Appendix B: Additional Figures

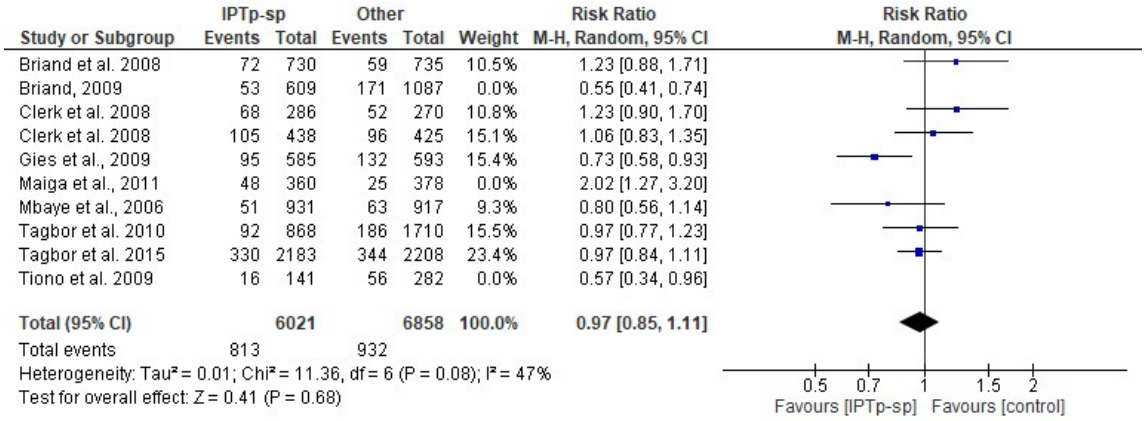
- Figure 6 Meta-Analysis of spontaneous abortion



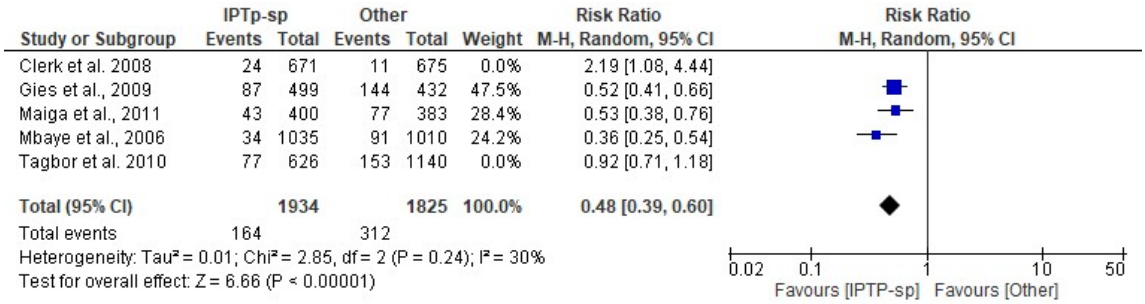
- Figure 7 Meta-analysis of Neonatal death



- Figure 8 Sensitivity analysis LBW omitting three studies



- Figure 9 Sensitivity analysis Maternal Parasitemia omitting two studies



Appendix C: Approved research protocol

Background

Introduction

Malaria in pregnancy (MIP) is a substantial public health burden that contributes to the rising cases of maternal/infant morbidity and mortality in countries where malaria is endemic [37]. The prevalence of MIP is a direct function of the intensity of transmission. Places that are malaria endemic are areas where there are very high rates of infection in the community (>60 percent of children below the age of 5 are infected) but the exposure to the parasite is stable [38]. This means that women in these areas are likely to have frequent malaria episodes during their lifetime also an increased immunity hence milder complications [38].

This is in contrast to mesoendemic malaria areas, which refers to places where transmission is lower(<20 percent of children below the age of 5 are infected) but the exposure to the parasite is more unstable, the resultant effect of which is a decreased development of natural immunity [38]. This means pregnant women residing in these areas are more likely to develop more serious complications such as hypoglycaemia and pulmonary oedema [39].

Due to the progressively varied development of the female immune system in the course of pregnancy, and the proliferation of the placenta that acts as a new organ bringing about novel places for parasites to bind to, women who are pregnant forfeit a fraction of their immunity [6]. Pregnant women are uniquely prone to severe *Plasmodium falciparum* malaria [37]. Erythrocytes infected with *P.falciparum* segregate when in the placenta thus interfering with the flow of nutrients from the mother to foetus hence resulting in intrauterine growth retardation [37]. Hence, malaria is linked to an increased risk of abortion, still birth and low birth weight [31].

Malaria is ranked second in terms of death as a result of infection in the world after tuberculosis, it is estimated to infect between 350 – 500 million people yearly and accounts for 1 – 3 million deaths per year [40]. Malaria is the cause of over 10,000 maternal and 200,000 neonatal deaths per year globally[41].

The effect of malaria in West Africa is highly disproportionate when compared to other regions accounting for 50% of the burden [42]. Greater than 300 million people in West Africa are at risk, being in an area of high transmission [42]. The percentage of maternal deaths as a result of direct or indirect malaria fall within 0.5% to 23% in hospital reported cases, this figure ranges between 2.9 – 17.6% in community reported cases [42]. In endemic West Africa it is estimated that with a 5% prevalence of severe malaria, there are maternal deaths per 100,000 live births related to severe anaemia as a result of malaria [42].

Intermittent preventive therapy of malaria in pregnancy(IPTP) is essentially the administration of a single dose of the Sulphadoxine/Pyrimethamine (SP) combination anti-malarial medication at least twice during pregnancy disregarding the status of current infection [7]. In areas where malaria infections are common, malaria during pregnancy may constitute up to 15% of anaemia during pregnancy, 5 – 14% of underweight births and 30% of avoidable low birth weight [8]. Because of the simple fact that MIP can bring about adverse effects on the unborn foetus as well as the mother [5], producing effects which include maternal anaemia, foetal loss, premature delivery, intra-uterine growth delay as well as births of infants with low birth-weights which ultimately is a risk factor that can lead to death [6]. In April 2000, the African summit on RBM held in Abuja Nigeria had adopted the Abuja Declaration, seeing the leaders of various regions of the African continent committing to making sure that 60% of pregnant women in malaria-endemic areas area able to access effective prevention [41].

The Abuja declaration of 2000 aimed to achieve the aforementioned by enhancing easier access to the right, cost effective and relevant treatment within a 24 hour time period on seeing the symptoms; promoting the access to the right mix of personal and protective measures that are usually common within communities, such as the use of insecticide-treated nets(ITNs); and promoting the prophylactic use of IPTP-SP especially for those experiencing their first

pregnancies [41]. A combination of IPTP-SP and ITNs are routinely dispatched through antenatal clinics (ANCs) usually as an end result alliance between malaria control programmes and reproductive health programmes implemented at country level [43].

Literature review

During pregnancy, the prevention of malaria is important in order to reduce peripheral and placental infection and the subsequent maternal morbidity. Prophylactic antimalarial medication is therefore recommended; mefloquine and chloroquine chemoprophylaxis have seen wide implementation throughout much of West Africa [44]. Even with the increasing regional conformity concerning the effectiveness of IPTP-SP in preventing adverse outcomes of MIP, the uptake of IPTP-SP was largely concentrated in East Africa where the original studies were initially conducted [9].

The use of SP to prevent malaria infection in pregnancy has shown much merit, Menéndez et al. in 2010 found out through a randomized placebo-controlled trial (RCT) that assessed the effectiveness of 2 doses of IPTP-SP, that it reduced neonatal mortality by 61%. IPTP-SP prevents the adverse consequences of malaria on maternal and fetal outcomes, such as placental infection, clinical malaria, maternal anemia, fetal anemia, low birth weight and neonatal mortality.

In a 2013 systematic review and meta-analysis of IPTP-SP trials that compared ≥3-dose SP regimens with the standard 2-dose SP regimen.The≥3-dose SP regimens resulted in fewer low birth weight infants (RR 0.80, 95% CI 0.69-0.94;134/1000 against 167/1000). And less moderate to severe maternal anemia (RR 0.60, 95% CI 0.36-0.99; 22/1000 against 36/1000) as well as less placental malaria (RR 0.51, 95% CI 0.38-0.68; 32/1000 against 63/1000) [34].

This systematic review sheds significant light on the overall IPTP-SP effectiveness in Africa. Using seven trials in its analysis, it has shown that a ≥3-dose regimen of SP is better tolerated. When considering that the number of trials were limited, it begs to investigate whether the

results are truly generalizable given that the transmissibility of malaria varies across regions as well as the differing rate of conceptions across the said regions.

Studies that have assessed the effectiveness of IPTP in West Africa have taken the form of randomized control trials as well as cross sectional studies. In 2015, a study carried out in Ghana explored the prevalent use of SP for IPTP, in order to assess its effectiveness. This cross-sectional study examined the prevalence of IPTP-SP usage for prevention of malaria among pregnant women as well as evaluated factors associated with IPTP-SP use during pregnancy in Sekondi-Takoradi region of Ghana [45]. Analysis of the results showed that pregnant women in their third trimester who received ≥2 doses of SP showed decreased likelihoods of malaria (adjusted OR, 0.042; 95% CI, 0.003-0.51)[45].

In a similar vein, another research study carried out in Ghana in 2008 examined the effectiveness of sulphadoxine-pyrimethamine (SP) for IPTP, alone and in combination with amodiaquine (AQ) in form of an RCT. As outcomes the trial looked at incidences of anemia and low birth-weights amongst others, the study found out that there was no difference in the overall effectiveness when SP was combined with AQ or used alone as they had similar outcomes on maternal anemia and low birth-weights[20]. An important conclusion derived from the aforementioned studies is that IPTP regimens that contain AQ are a potentially useless alternative as compared to IPTP-SP due mostly to the adverse events as a result of the AQ.

Even with the spread of SP resistance, IPTP-SP has shown consistency in providing noteworthy benefit, with a resultant protection against neonatal mortality (protective effectiveness 18%) and 21% reduction in LBW under routine programme conditions [46]. This study used a retrospective cohort from national cross-sectional datasets sourced from 25 African countries within a follow up time of 10 years. The study found that full malaria prevention with IPTP was associated with decreased risk of neonatal mortality. Again, the generalizability of this study is questioned due here in part due to bias and potential confounding by matching women

on factors assumed to be associated with access to malaria prevention in pregnancy across the transmissibility regions as well as birth outcomes.

A study in Benin has showed that, despite the presence of molecular markers of resistance in the malaria parasite, SP remained efficacious [3]. This study however showed that the adverse effects of malaria remained until birth and eventually showed that the adverse effect of malaria is more pronounced in the fetal growth rate of women with a low anthropometric status i.e. a low estimated pre-pregnancy weight and low birth weight during pregnancy [3]. Although this study was carried out in Benin, with evidence of molecular markers of resistance, it holds sway to assume that in different regions of West Africa resistance could be a factor as rates of transmission although high throughout the year[7], it can fluctuate in different regions and could potentially be different were the study located elsewhere.

Problem statement

In sub-Saharan Africa, thirty countries account for 90% of all deaths attributed to malaria globally [1]. In West and Central Africa, the combined burden of malaria in the Democratic Republic of Congo and Nigeria accounted for more than 40% of all deaths attributed to malaria [2].

Every year, roughly 25 million African women who reside in malaria-endemic areas become pregnant and therefore become at risk of *P.falciparum* malaria infection during their pregnancy [4]. The end result which is basically the impairment of fetal nutrition is essentially what leads to LBW [47], which is a prime cause of a low rate of infant survival and development in Africa [48]. Coupled with the fact that, recent studies in the region have shown the propensity of SP resistance, by *P.falciparum* malaria; as characterized by the presence of molecular biomarkers of resistance on the parasite.[3].

The IPTP-SP intervention is currently employed as a 2 dose standard regimen in countries across West Africa [9]. When considering the all year round transmission as well as

the potential for resistance, the standard 2 dose may be inadequate in providing protection in the time period of 4-10 weeks of pregnancy which is a critical period for fetal weight gain.

Justification

In several countries in Africa, some *P. falciparum* parasites has been shown to carry quintuple mutations linked to SP resistance – which are linked to in-vivo therapeutic failure to SP. Nevertheless, recent evidence suggests that IPTP-SP is still very effective in preventing the adverse effects of malaria on maternal and fetal outcomes in areas where a high proportion of *P. falciparum* parasites carry these mutations[49]. A specific regional assessment (especially in the all year round transmission zone of West Africa) of the effectiveness of IPTP-SP is warranted in order to account for possible loss in effectiveness due to a rise in *P.falciparum* resistance and/or the low uptake of the intervention.

Two years prior to the adoption of the Abuja declaration in 2000, the roll back malaria (RBM) partnership was already in effect in many countries in West Africa. The overall strategy of the RBM is to reduce malaria morbidity and mortality by attaining universal coverage and health systems strengthening [50]. Although there has been a significant increase in investment in IPTP programs and despite the recorded higher rates of attendance at ANC clinics, the uptake of IPTP-SP remains low [51] and the adverse effects of MIP continues to pose a significant problem.

In Nigeria for instance IPTP-SP was instituted in 2001, nevertheless coverage is still quite low in both the first and second doses of administration at 8.0% and 4.6% respectively [10].

Research objective

To conduct a systematic review and meta-analysis of trials in order to determine and assess the effectiveness of the standard 2-dose IPTP regiment in populations of pregnant women in West

Africa, and explore the association of the intervention with a lower risk of low birth weight. The specific objective of this review is:

1. Assess the effectiveness of IPTP-SP interventions in West Africa.

In addition, the meta-analysis will:

1. Estimate the combine the effect sizes of the studies using a weighted average in order to show if the outcome of MIP is more varied than expected.

Analyze the heterogeneity of the studies by showing the importance of the effect size of the IPTP-SP studies by using forest plots.

Methodology

Study design

This systematic review and meta-analysis protocol follows a design based on the guidelines from the preferred Reporting Items for Systematic reviews and Meta-analysis protocol(PRISMA-P) Criteria for considering studies for the review [18].

Study population and sampling

The study population will be pregnant women, in all socio economic strata who have access to ANC services and any MIP interventions that has included IPTP. The sampling will be restricted to particular studies in question.

Intervention

The review will examine interventions that take the form of the WHO MIP policy of the administration of 2 doses of IPTP at the second or third trimester of pregnancy [49]. The review will take into consideration, randomized control trial studies that evaluate the effectiveness of receiving IPTP-SP as a malaria prevention intervention.

Search strategy

The PICO (patient, intervention, comparator and outcome) framework will be used to identify applicable terminology for use in the review as inclusion in the search strategy[52]. The

combination of keywords relating principally with the intervention and outcome will comprise the search terms.

A step wise, systematic and extensive literature search of online databases will be performed based on the identified search terms. This search strategy will include the MIP online Library as well as PubMed and Google scholar.

Inclusion criteria
This review aims to include;

- Published and unpublished original research studies.
- Randomized or quasi-randomized controlled trials that have been carried out with pregnant women living in West Africa
- Published in either French and/or English
- published between 2005 and 2017
- Conducted in all parts of West Africa.

Exclusion criteria
This review aims to exclude;

- Studies that includes other prophylactic anti-malarial agents
- Studies that are not in line with the WHO roll back malaria policies
- Studies that focus on the beneficial effects of folic acid
- Studies that looked at the treatment of Malaria in pregnancy rather than the prevention

Comparator
Studies that include a comparator will not be discriminated against; the comparator will essentially be the population of which the study outcomes did not reflect but belong to the study.

Outcome
The primary outcome measure is LBW and mean birth weight, the secondary outcomes include maternal anemia as gauged by maternal hemoglobin level i.e. levels less than 11g/dl as low, 6

– 8 g/dl for moderate to severe anemia. Other outcomes include maternal malaria infection, spontaneous miscarriage, and neonatal death.

Data collection

Data extraction and management

Data extraction will be conducted independently by two investigators who will employ a specially designed standardized data extraction forms. The principal investigators of identified studies will only be contacted if pertinently required information is missing. For any and all studies that will be searched for, the following information will be extracted.

- Author
- Publication year
- Year of study start and end
- Design of study
- Process of randomization
- Local malaria transmission
- Details of study groups
- Number of women enrolled
- Outcomes assessed(stratified by sub group)

Data synthesis and analysis

The meta-analysis of data on the effectiveness of the IPTP-SP interventions will be conducted using Review Manager Version 5.3.5(Cochrane Collaboration Software) where summary risk ratios (RRs) of observing adverse effects will be calculated using random effects model. It is expected that effectiveness studies will provide results for the 2 tier doses of IPTP-SP. Studies will be assigned a score based on the quality assessment, the I^2 and 95% confidence intervals will be used to quantify heterogeneity.

Results that show heterogeneity between 25 and 50% will be indicative of moderate heterogeneity, from 50 – 75% will show substantial heterogeneity and above 75% will be of

significant heterogeneity.

Although Quantitative synthesis will be the preferred approach, if the number of studies found does not allow for this or if heterogeneity is observed to be too high or unexplained, then a narrative synthesis will be performed instead.

The findings of this review will be reported in conformity with the PRISMA guidelines [18].

Quality and bias assessment of included studies

The quality of each study will be assessed using the Cochrane Public health reviews Groups' recommended Effective public health Practice Project Quality assessment tool for quantitative studies[19]. The tool guides the selection of studies towards adequate representation of samples as they relate to the comparison of baseline groups, the quality data collection and the rate at which participants leave the study without duly been observed for the effect looked out for. The tool for assessing the risk of bias will be used to determine the quality of included studies as low (high risk of bias) and high (low risk of bias) or not applicable. Any discrepancies will be discussed and resolved by agreement on part of the reviewers and if there is need, a third reviewer will be consulted in case of an impasse.

Reporting

This review will be reported according to the Preferred Reporting Items for systematic reviews and Meta-analysis (PRISMA) guidelines[18]. Flow diagrams will be used to summarize the eligibility criteria and selection process used. Supplementary documents will also be published and these will include the tools employed for quality appraisal assessments and the search strategies.

Limitations

The source and quality of data from the primary studies may limit its validity. Studies from other countries follow policy guidelines that are specific to that country and may distort the base for comparison. The studies will come in either French or English language some context could be lost in translation.

Ethical considerations

In the interim, there have been no ethical barriers foreseen, given that this is a protocol for a systematic review of published studies. The results of this study will be published in a peer-reviewed journal and presented at conferences.

Search table: MeSH terms

SEARCH	***MeSH term(modified as needed for use in other databases)***
#1	*Effectiveness*
#2	*Efficacy*
#3	***#1 OR #2***
#4	*"Intermittent preventive therapy in pregnancy"*
#5	*Sulphadoxine Pyrimethamine*
#6	*Fansidar*
#7	***#4 OR #5 OR #6***
#8	*Risk*
#9	*Incidence*
#10	***#8 OR #9***
#11	*"Adverse Birth Outcomes"*
#12	*Low Birthweight*
#13	*Maternal Parasitemia*
#14	*Maternal Anemia*
#15	*Spontaneous Abortion**
#16	*Neonatal death*
#17	*Malaria in Pregancy*
#18	***#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17***
#19	*Randomized controlled trial*
#20	*Controlled clinical trial*
#21	*Randomized*
#22	*Placebo*
#23	*Clinical trials as topic*

#24	*West African search filter (Appendix A)*
#25	***#19 OR #20 OR #21 OR #22 OR #23 OR #24***
#26	#3 AND #7 AND #10 AND #18 AND #25

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Appendix C: Approved ethics waiver

Human Research Ethics Committee (Medical)

Golden Jubilee: October 1966 – October 2016

Research Office Secretariat: Faculty of Health Sciences, Phillip Tobias Building, 3rd Floor, Office 301,
29 Princess of Wales Terrace, Partktown, 2193 Tel +27 (0)11-717-1252 /1234/2656/2700
Private Bag 3, Wits 2050, email: zanele.ndlovu@wits.ac.za
Office email: hrec-medical.researchoffice@wits.ac.za
Website: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

Ref: W-CJ-161118-2 18/11/2016

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: **Mr Oloche Emmanuel Otukpa (Student No 753575)**

Project title: **The effectiveness of intermittent preventive therapy in pregnancy with sulphadoxine and pyrimethamine (IPTP-SP) as a malaria prevention intervention and factors that affect its uptake in West Africa: a protocol for a systematic review and meta-analysis.**

Reason: This is a review of information in the public domain. There are no human participants.

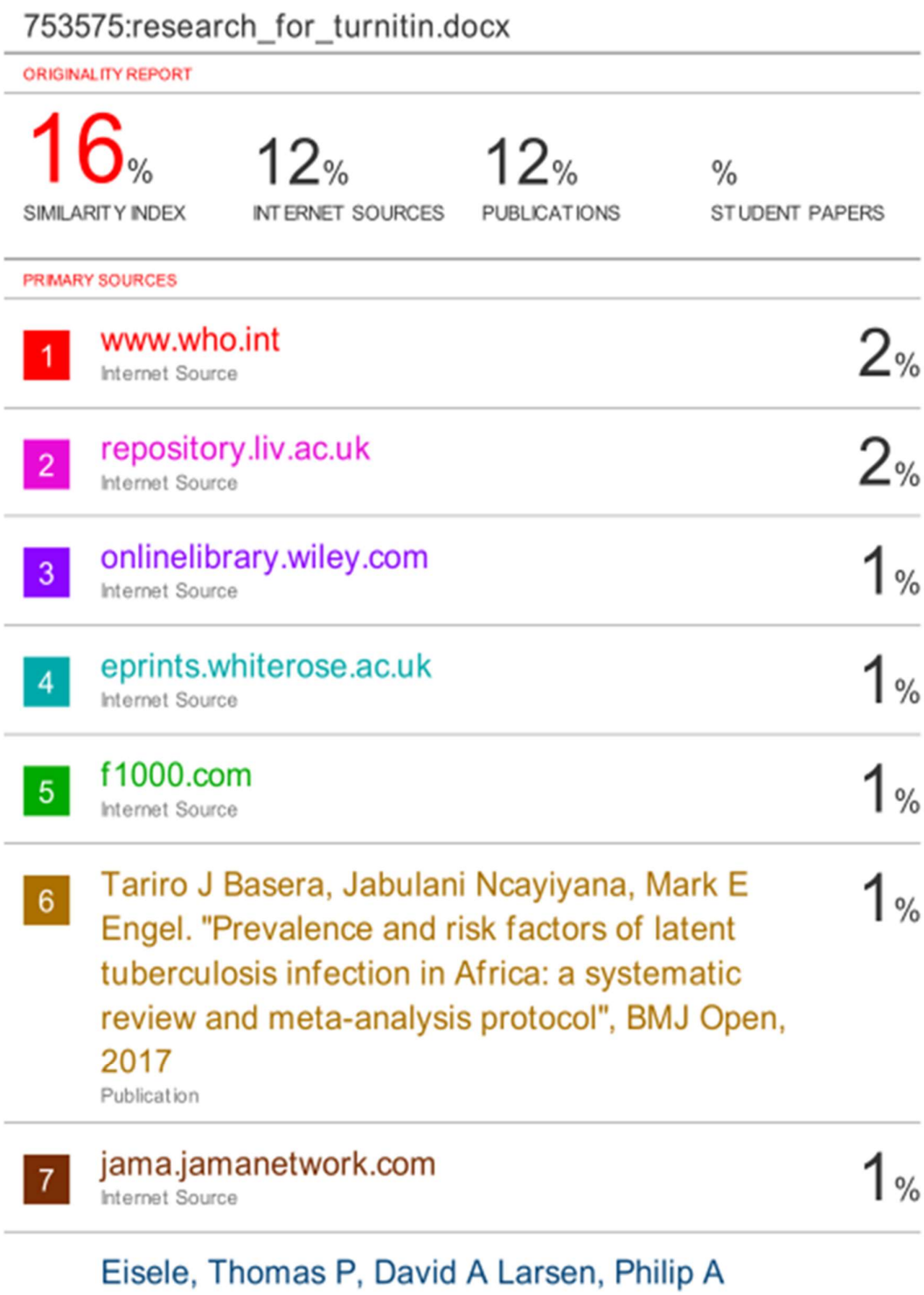
UNIVERSITY OF THE WITWATERSRAND
PROF PE CLEATON-JONES
HREC (MEDICAL)
2016 -11- 18
JOHANNESBURG

Professor Peter Cleaton-Jones

Chair: Human Research Ethics Committee (Medical)

Copy – HREC (Medical) Secretariat: Zanele Ndlovu, Rhulani Mkansi.

Appendix D: Turnitin plagiarism report



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5	f1000.com Internet Source	1%
6	Tariro J Basera, Jabulani Ncayiyana, Mark E Engel. "Prevalence and risk factors of latent tuberculosis infection in Africa: a systematic review and meta-analysis protocol", BMJ Open, 2017 Publication	1%
7	jama.jamanetwork.com Internet Source	1%

Eisele, Thomas P, David A Larsen, Philip A

Appendix E: Author's guidelines for publication (BMC malaria Journal)

Submission guidelines

Our 3-step submission process

1.

Before you submit
Now you've identified a journal to submit to, there are a few things you should be familiar with before you submit.

- Make sure you are submitting to the most suitable journal - Aims and scope
- Understand the costs and funding options - Fees and funding
- Make sure your manuscript is accurate and readable - Language editing services
- Understand the copyright agreement - Copyright

2.

Ready to submit
To give your manuscript the best chance of publication, follow these policies and formatting guidelines.

- *Malaria Journal* publishes the following article types:
  - Research article
  - Case report
  - Case study
  - Commentary
  - Meeting report
  - Methodology
  - Opinion
  - Review
  - Editorial

Click the relevant link to find style and formatting information for the article you are going to submit.

- General formatting rules for all article types - Preparing your manuscript
- Make sure your submission is complete - Prepare supporting information
- Copyright and license agreement - Conditions of publication
- Read and agree to our Editorial Policies - Editorial policies

3.

Submit and promote

After acceptance, we provide support so your article gains maximum impact in the scientific community and beyond.

Please note that manuscript can only be submitted by an author of the manuscript and may not be submitted by a third party.

- Who decides whether my work will be accepted? - Peer-review policy
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Submit your manuscript in Editorial Manager

Research article

Criteria

Malaria Journal publishes primary research articles from the full spectrum of malaria research. Subjects covered include any aspects of the biology of malaria parasites and their vectors; clinical features and disease pathophysiology; biochemistry and molecular biology; case management and treatment; drug development and drug resistance; immunology, immunogenetics and vaccine development; genomes and transcriptomes of malaria parasites and their vectors; epidemiology and transmission dynamics; vector control; health system, policy and planning issues relating to prevention and treatment; economic, sociological and anthropological issues; poverty and gender issues, land use and global environmental change; intersectoral issues; intervention studies and operational research; control policy and planning.

Malaria Journal requires that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's information on recommended repositories.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design
- list the full names, institutional addresses and email addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Results:** the main findings
- **Conclusions:** a brief summary and potential implications

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary.

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

For research articles this section should discuss the implications of the findings in context of existing research and highlight limitations of the study. For study protocols and methodology manuscripts this section should include a discussion of any practical or operational issues involved in performing the study and any issues not covered in other sections.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study to the field.

Methods (can also be placed after Background)

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each authors' competing interests int his section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

See our editorial policies for a full explanation of acknowledgements and authorship criteria.

If you do not have anyone to acknowledge, please write "Not applicable" in this section.

Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the

submission system and also include collaborating author names as the last paragraph of the “Acknowledgements” section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

Please note that individual names may not be present in the PubMed record at the time a published article is initially included in PubMed as it takes PubMed additional time to code this information.

Authors' information

This section is optional.

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission.

Examples of the BioMed Central reference style are shown below. Please ensure that the reference style is followed precisely.

See our editorial policies for author guidance on good citation practice.

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link (e.g. for blogs) they should be included in the reference.

Example reference style:

Article within a journal
Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)
Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Med. 2013;11:63.

Article within a journal by DOI
Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement
Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book
Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)
Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored
Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document
Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

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Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

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Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site
Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site
Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site
ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier
Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

Figures, tables additional files

See General formatting guidelines for information on how to format figures, tables and additional files.

Appendix F: West African Search Filter (as used in the search strategy)

(‘‘Africa’’[MeSH] OR Africa*[tw] OR tw Benin[tw] OR ‘‘Burkina Faso’’[tw] OR ‘‘Cape Verde” OR Gambia[tw] OR Ghana[tw] OR Guinea[tw] OR ‘‘Guinea Bissau’’[tw] OR ‘‘Ivory Coast’’[tw] OR ‘‘Cote d’Ivoire’’[tw] OR Liberia[tw] OR Mali[tw] OR Mauritania[tw] OR Niger[tw] OR Nigeria[tw] Senegal[tw] OR ‘‘Sierra Leone’’ OR Togo[tw] OR ‘‘West African’’[tw] OR ‘‘Western Africa Western African’’[tw])