INTERMITTENT PREVENTIVE TREATMENT FOR MALARIA AND OUTCOMES OF MALARIA IN PREGNANCY: A SYSTEMATIC REVIEW PROTOCOL

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Abstract: **Malaria is a public health problem globally especially in the Sub-Saharan Africa and among the under five children and pregnant women and is associated with a lot of maternal and foetal complications. We will conduct a systematic review of all studies on the effect of intermittent preventive treatment on the prevalence and outcomes of malaria in pregnancy. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and study quality will be assessed by the Jadad score in addition to an evaluation of allocation concealment and data analysis. If sufficient data are available, a meta-analysis will be conducted. The effect sizes will be generated using Hedges' g score, for both fixed and random effect models. I^2 statistics and Galbraith plots will be used to assess heterogeneity and identify their potential sources. Potential publication and small sample size bias will be assessed by visual inspections of funnel plots and also Egger's test. Subgroup analysis, conditional on number of studies retrieved and their sample size, will be stratified on IPT and malaria in pregnancy outcomes. Overall, the review will complement the evidence base on the benefits of intermittent preventive treatment in malaria.**

Keywords: **malaria, pregnancy, preventive treatment, sulfadoxine-pyrimethamine.**

1. INTRODUCTION

Malaria is a disease of global public health importance, caused by protozoan parasites of the genus Plasmodium. The epidemiology of malaria is rapidly changing and elimination may be feasible in some endemic regions within the next decade. Over 90% of the malaria burden is borne by populations in sub-Saharan Africa where *Plasmodium falciparum* is predominant and the high-risk groups include young children and pregnant women.(1) Malaria infection during pregnancy is most prevalent at the time of the first antenatal visit and these infections early in pregnancy have been associated with consequences for maternal and fetal well-being such as low birthweight, maternal anaemia and intra-uterine growth restriction.(2,3) Each year, 25–30 million women become pregnant in malaria-endemic areas of Africa, and similar numbers are exposed to malaria in Asia, Oceania, and South America.(4,5) Malaria is an important cause of severe anemia in pregnant African women, and by this mechanism malaria causes an estimated 10,000 maternal deaths each year.(6) Moreover, malaria infections result in 75,000–200,000 low birth weight (LBW) babies each year, due to combinations of preterm delivery (PTD) and fetal growth restriction (FGR).(7) Malaria remains one of the most

preventable causes of adverse birth outcomes. Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine–pyrimethamine is used to prevent malaria.(8,9) In malaria-endemic areas in Africa, intermittent preventive treatment with sulfadoxine-pyrimethamine (SP-IPTp) is recommended for all pregnant women in their first or second pregnancy.(10) Dosing should start in the second trimester and doses should be given at least 1 month apart, with the objective of ensuring that at least three doses are received.(11) Understanding of the pathogenesis of malaria in pregnancy has improved significantly in recent years, but important gaps remain. Emerging knowledge of the preventive treatment of malaria in pregnancy could improve maternal outcomes for pregnant women in malaria endemic areas.

Statement of the Problem

Pregnant women are 3 times more likely to suffer from severe disease as a result of malarial infection compared with their nonpregnant counterparts, and have a mortality rate from severe disease that approaches 50%.(7,12) In areas endemic for malaria, it is estimated that at least 25% of pregnant women are infected with malaria, with the highest risk for infection and morbidity in primigravidas, adolescents, and those coinfected with HIV.(9,13,14) The second trimester appears to bring the highest rate of infection, supporting the need for antepartum care as part of malarial prevention and treatment efforts. Literature showed that an estimated 125 million women become pregnant every year in malaria-endemic regions, with more than 85 million at risk of malaria.(1,15) All pregnant women are not equally susceptible to malaria; the susceptibility and severity of pregnant women to malaria is attributable to varying factors which include immunological and humoral changes, parity, maternal age, gestational age and intensity of transmission.(16) About twenty-five million pregnant women are currently at risk for malaria, and, according to the World Health Organization (WHO), malaria accounts for over 10,000 maternal and 200,000 neonatal deaths per year.(17) Despite the intervention of intermittent preventive treatment, there is little information on the impact of intermittent preventive treatment on malaria in pregnancy.

Justification of the Review

The high prevalence of malaria in Nigeria motivated the government to institute the National Malaria Control Strategic Plan, whose aim is to reduce the malaria burden to pre-elimination levels and bring malaria-related mortalities to zero.(18,19) This includes addressing national health and development priorities including the Roll Back Malaria goals, the Millennium Development Goals and Sustainable Development Goals.(20–22) Prevention and treatment of malaria in pregnancy was included as one of the approaches to the implementation and actualization of this agenda.(19,23) In addition, adoption of prevention of malaria in pregnancy interventions using long-lasting insecticide-treated nets (LLITNs), intermittent preventive treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP), and case management following laboratory diagnosis is in line with the National Malaria Strategic Plan and the global action for a malaria-free world.(24,25) Therefore this study was conceptualized to monitor the prevalence of malaria in pregnancy and make a projection for the years ahead using Plateau State malaria case-based surveillance data. The analysis of malaria in pregnancy case-based surveillance will provide an insight into the effect of intermittent preventive treatment on the epidemiology of malaria in pregnancy.

Research Question

What is the effect intermittent preventive treatment for malaria on the prevalence of malaria in pregnancy?

2. METHODS

Search strategy

The search strategy will be performed using resources that enhance methodological transparency and improve the reproducibility of the results and evidence synthesis. In this sense, the search strategy will be elaborated and implemented prior to study selection, according to the PRISMA-P checklist as guidance.(26) Additionally, using the Population, Intervention, Comparison, Outcome and Study design (PICOS) strategy.(26) The guiding question of this review in order to ensure the systematic search of available literature will be: *'Has the intermittent preventive treatment for malaria reduced the prevalence of malaria in pregnancy?'* Studies will be retrieved using eight databases: MEDLINE (via PubMed), Web of Science, Cochrane Library, Science Direct, PsycINFO, CINAHL, LILACS and SciELO. will be performed. There will be no restriction regarding the language to avoid the reduce the yield of appropriate articles and

also generalizability. In addition, the reference section in the studies returned by the above search was scrutinised for additional relevant articles. Initially, the existence of controlled descriptors (such as MeSH terms, CINAHL headings, PsycINFO thesaurus and DeCS-Health Science Descriptors) and their synonyms (key words) will be verified in each database. The search terms will be combined using the Boolean operators 'AND' and 'OR'. Subsequently, a search strategy combining MeSH terms and free-text words (Table 1) will be used. In order to locate the quasi-experimental studies. In order to locate the clinical trials and experimental studies, a filter after the PICOS search strategy will be added to include the following terms: AND (randomized controlled trial OR randomized controlled trials as topic OR controlled clinical trial OR clinical trial OR nonrandomized controlled trials).

Table 1: MeSH Terms for Literature Search

S/No.	Item	MeSH keywords
1	Malaria in Pregnancy	Malaria, Fever, Pregnancy, gravid, plasmodium falciparum, prevalence, epidemiology, incidence, distribution
2	Intermittent preventive treatment	Prevention, intermittent preventive therapy, sulfadoxine-pyrimethamine chemotherapy.

Study selection criteria

A summary of the participants, interventions, comparators and outcomes considered, as well as the type of studies included according to PICOS strategy, is provided in Table 2.

Table 2: Inclusion criteria for study selection

Item	Inclusion Criteria
Population	Pregnant women
Intervention	Intermittent preventive treatment
Comparison	No treatment
Outcome	1. Prevalence of malaria 2. Outcome of malaria in pregnancy
Study Design(s)	Randomized clinical trials and Quasi-experimental studies

Screening and data extraction

Initial screening of studies will be based on the information contained in their titles and abstracts and will be conducted by two independent investigators. When the reviewers disagreed, the article will be re-evaluated and, if the disagreement persisted, a third reviewer will make a final decision. Full-paper screening will be conducted by the same independent investigators. Cohen's kappa will be used to measure inter-coder agreement in each screening phase. Data will be extracted using a previously proposed tool,(26) including four domains: (1) identification of the study (article title; journal title; impact factor of the journal; authors; country of the study; language; publication year; host institution of the study (hospital; university; research centre; single institution; multicentre study)); (2) methodological characteristics (study design; study objective or research question or hypothesis; sample characteristics, e.g. sample size, sex; age; race; acute and/or chronic diagnoses; groups and controls; stated length of follow-up; validated measures; statistical analyses, adjustments; (3) main findings and (4) conclusions. If the outcome data in the original article were unclear, the corresponding author will be contacted via email for clarification. For data extraction, two independent Microsoft Excel spreadsheets will elaborated for two reviewers to summarise the data from the included studies. Then, the spreadsheets were combined into one. Disagreements will be resolved by a third investigator.

Quality assessment

Methodological quality of the RCTs will be assessed using the Jadad Scale,(26) a widely used tool for classification of the quality of the evidence from RCTs. The Jadad Scale scores range from 0 to 5, with studies scoring <3 considered as low quality and studies that score ≥3 classified as high quality.**Error! Bookmark not defined.** The internal validity and risk of bias for RCTs will be assessed with the appraisal tool from the Cochrane Handbook for Systematic Reviews of

Interventions V.5.1.0,46 which assesses the following study-level aspects: (1) randomisation sequence allocation; (2) allocation concealment; (3) blinding; (4) completeness of outcome data and (5) selective outcome reporting; and classifies studies into low, high or unclear risk of bias. For assessing NRCT, the ROBINS-I, a recently developed tool, will be used.(26) ROBINS-I is particularly useful to those undertaking systematic reviews that include non-randomised studies of interventions. This tool is guided through seven chronologically arranged bias domains (pre-intervention, at intervention and post-intervention), and the interpretations of domain-level and overall risk of bias judgement in ROBINS-I are classified in low, moderate, serious or critical risk of bias.**Error! Bookmark not defined.**

Two independent reviewers will assess the methodological quality of eligible trials. Two independent reviewers will score the selected studies and disagreements will be resolved by a third reviewer. The risk of bias for each outcome across individual studies will be summarized as a narrative statement, and supported by a risk of bias table. A review-level narrative summary of the risk of bias will also be provided.

3. CONCLUSION

This systematic review will provide evidence in support or against the hypothesis that intermittent preventive treatment has been effective in preventing malaria in pregnancy. This conclusion will stem from direct assessment of the prevalence of malaria in pregnant women and the outcomes of pregnancy after receiving intermittent preventive treatment. Where sufficient data are available, we will conduct a meta-analysis to confirm the relationship between the prevalence of malaria in pregnancy and intermittent preventive treatment. Overall, the review will complement the evidence base on the benefits of intermittent preventive treatment in malaria.

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