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Coinfections of malaria and sexually transmitted and reproductive tract infections in pregnancy in sub-Saharan Africa: a systematic review and individual participant data meta-analysis protocol

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ABSTRACT

Introduction Malaria infection and curable sexually transmitted infections and reproductive tract infections (STIs/RTIs) adversely impact pregnancy outcomes. In sub-Saharan Africa, the prevalence of malaria and curable STIs/RTIs is high and, where coinfection is common, combination interventions may be needed to improve pregnancy outcomes. The aim of this systematic review is to estimate the prevalence of malaria and curable STI/RTI coinfection during pregnancy, risk factors for coinfection and prevalence of associated adverse pregnancy outcomes.

Methods and analysis We will use three electronic databases, PubMed, EMBASE and Malaria in Pregnancy Library to identify studies involving pregnant women attending routine antenatal care facilities in sub-Saharan Africa and reporting malaria and curable STI/RTI test results, published in any language since 2000. We will search databases in the second quarter of 2023 and repeat the search before completion of our analyses. The first two authors will screen titles and abstracts, selecting studies that meet inclusion criteria and qualify for full-text screening. If agreement on inclusion/exclusion cannot be reached, the last author will serve as arbiter. We will extract data from eligible publications for a study-level meta-analysis. We will contact research groups of included studies and request individual participant data for meta-analysis. The first two authors will conduct a quality appraisal of included studies using the GRADE system. The last author will adjudicate if the first two authors do not agree on any appraisals. We will conduct sensitivity analyses to test the robustness of effect estimates over time (by decade and half-decade periods), geography (East/Southern Africa vs West/Central Africa), gravidity (primigravidae, secundigravidae, multigravidae), treatment type and dosing frequency, and malaria transmission intensity.

Ethics and dissemination We obtained ethics approval from the London School of Hygiene & Tropical Medicine (LSHTM Ethics Ref: 26167). Results of this study will be disseminated via peer-reviewed publication and presentation at scientific conferences.

PROSPERO registration number CRD42021224294.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analyses will be reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
⇒ The GRADE system will be used to assess the quality of studies from which data have been extracted.
⇒ *Plasmodium falciparum* parasite rate estimates among 2–10 years, as generated by Malaria Atlas Project, have been used previously as a proxy for malaria infection among pregnant women, and will be applied as available for the years that studies were conducted to stratify the effects of malaria transmission intensity on coinfection prevalence.
⇒ Article screening and data extraction, with assessment of eligibility or quality appraisal, will be conducted by the first two authors to be adjudicated by the last author.
⇒ We will conduct an individual participant data meta-analysis, allowing for adjustment of individual and study characteristics in calculating the measures of disease burden.

INTRODUCTION

Malaria infection and curable sexually transmitted infections and/or reproductive tract infections (STIs/RTIs) can adversely impact pregnancy outcomes and are important to address as part of the antenatal care package in countries where prevalence is high. In areas where coinfection is common, combined interventions may be required to improve pregnancy outcomes. A systematic review and

meta-analysis of studies between 1990 and 2011 found the prevalence of placental malaria among women attending antenatal care 25.8% (95% CI 19.7% to 31.9%) in East and Southern Africa and 39.9% (95% CI 34.2% to 45.7%) in West and Central Africa.[1] The same analysis reported the prevalence of curable STIs/RTIs in East Africa: syphilis, 4.5% (95% CI 3.9% to 5.1%;), gonorrhoea, 3.7% (95% CI 2.8% to 4.6%), chlamydia, 6.9% (95% CI 5.1% to 8.6%), trichomoniasis, 29.1% (95% CI 20.9% to 37.2%) and bacterial vaginosis, 50.8% (95% CI 43.3% to 58.4%). In West and Central Africa, prevalence estimates were as follows: syphilis, 3.5% (95% CI 1.8% to 5.2%), gonorrhoeae, 2.7% (95% CI 1.7% to 3.7%), chlamydia, 6.1% (95% CI 4.0% to 8.3%), trichomoniasis, 17.8% (95% CI 12.4% to 23.1%), bacterial vaginosis, 37.6% (95% CI 18.0% to 57.2%). Importantly, not one of the 171 studies identified by this systematic review reported the prevalence of malaria and curable STI/RTI coinfection. Prompted by this dearth of coinfection estimates, investigators conducted an observational cohort study of pregnant women attending antenatal care (N=1084) in rural Zambia between 2013 and 2014. At antenatal care booking, 38.7% (n=414) had a malaria infection and at least one STI/RTI, 26.0% (n=278) had an STI/RTI only, and 18.9% (n=202) had malaria only.[2]

Malaria infection during pregnancy increases the risk of delivering a low birth weight (LBW) newborn 2.06 times (IQR 1.76–2.27).[3] The 2020 World Malaria Report estimated that malaria in pregnancy was responsible for 818 727 LBW (<2.5 kg) babies in sub-Saharan Africa.[4] Meta-analysis has shown that maternal malaria infection increases the odds of preterm delivery more than threefold (OR 3.08; 95% CI 2.32 to 4.10),[5] and nearly doubles the odds of stillbirth (OR 1.95; 95% CI 1.48 to 2.57).[6] Globally, the attributable fraction of stillbirth to malaria is 8.0% and to syphilis is 7.7%.[7] An estimated 350 000 adverse pregnancy outcomes worldwide were attributable to syphilis, including 143 000 early fetal deaths/stillbirths, 62 000 neonatal deaths, 44 000 preterm/LBW babies and 102 000 infected infants, with the largest burden (64.0% of adverse pregnancy outcomes) in Africa.[8] A systematic review and meta-analysis found that gonorrhoea in pregnancy increased the odds of preterm birth (OR 1.55; 95% CI 1.21 to 1.99), perinatal mortality (OR 2.16; 95% CI 1.35 to 3.46), LBW (OR 1.66; 95% CI 1.12 to 2.48) and ophthalmia neonatorum (OR 4.21; 95% CI 1.36 to 13.04).[9] Chlamydia infection in pregnancy is associated with preterm premature rupture of membranes (OR 1.81; 95% CI 1.0 to 3.29), LBW (OR 1.34; 95% CI 1.21 to 1.48) and being small for gestational age (OR 1.14; 95% CI 1.05 to 1.25).[10] Meta-analysis has shown that trichomoniasis during pregnancy increases the risk of preterm birth (risk ratio (RR) 1.42; 95% CI 1.15 to 1.75) and delivering small for gestational age infants (RR 1.51; 95% CI 1.32 to 1.73).[11] Bacterial vaginosis during pregnancy more than doubles the odds of preterm delivery (OR 2.19; 95% CI 1.54 to 3.12) and increases nearly 10-fold the odds of spontaneous abortion (OR 9.91; 95% CI 1.99 to 49.34).[12] A systematic review and meta-analysis reported that *Mycoplasma genitalium* infection during pregnancy was associated with more than double the odds of preterm birth (OR 2.34; 95% CI 1.17 to 4.71).[13]

The WHO currently recommends intermittent preventive treatment of malaria in pregnancy (IPTp) with sulfadoxine–pyrimethamine (SP) in all areas with moderate to high malaria transmission.[14] Recent evidence suggests that SP may also contribute to improving birth outcomes among women with curable STIs/RTIs. Evidence supporting this comes from the pregnancy cohort in Zambia noted above which found that women who, retrospectively, were found to have had curable STIs/RTIs at antenatal care booking, were subsequently protected by IPTp-SP against adverse pregnancy outcomes in a dose–response relationship.[15] Further evidence comes from randomised controlled trials (RCTs) that compared IPTp with SP against IPTp with dihydroartemisinin–piperaquine (DP).[16 17] Although DP was superior to SP in measures related to malaria infection, IPTp-SP was superior to IPTp-DP in terms of protecting against LBW and increasing birth weight overall.[16 17] A mediation analysis[18] of three RCTs[16 17 19] showed that IPTp-SP appears to have strong non-malarial effects on birth weight.[20 21] Despite the broad-spectrum effects of IPTp-SP, malaria parasites throughout sub-Saharan Africa, and in particular in East and Southern Africa, IPTp-SP is compromised as an antimalarial treatment and IPTp-SP is not indicated for the treatment of curable STIs/RTIs. Within this context, this study aims to estimate coinfection prevalence of malaria and curable STIs/RTIs, coinfection risk factors and coinfection associated pregnancy outcomes.

Aims and objectives

The aim of this study is to estimate the dual burden of malaria and curable STI/RTI among pregnant women attending antenatal care facilities in sub-Saharan Africa in papers published from 2000 to present. The objectives are to answer the following research questions:

1. What is the coinfection prevalence, defined as infection with malaria and at least one curable STIs/RTIs (syphilis, gonorrhoea, chlamydia, trichomoniasis, bacterial vaginosis or *M. genitalium* infection) among pregnant women in sub-Saharan Africa?
2. What are risk factors for malaria and curable STI/RTI coinfection?
3. What are the risks of any adverse pregnancy outcome (miscarriage, stillbirth, preterm delivery, LBW, small for gestational age) among women with a coinfection, as defined above, compared with women with just malaria or just curable STI/RTI or neither malaria nor any curable STI/RTI?

METHODS AND ANALYSIS

This systematic review will be reported following the Preferred Reporting Items for Systematic Review and

Meta-Analysis Protocols guidelines. We will conduct a study-level and individual participant data meta-analysis.

Inclusion/exclusion criteria

We will include studies involving pregnant women attending routine antenatal care facilities in sub-Saharan Africa and published in any language between 2000 and present that reported malaria and curable STI/RTI test results as well as pregnancy outcome. Studies will be excluded that focused exclusively on high-risk pregnant women (HIV-infected women, pregnant commercial sex workers, women with ectopic pregnancies) and/or cohorts of women presenting with a chief complaint of vaginal discharge, or data collected among postpartum women.

Intervention(s), exposure(s)

We will include studies that report malaria, syphilis, gonorrhoea, chlamydia, trichomoniasis, bacterial vaginosis or *M. genitalium* infection among pregnant women attending antenatal care facilities, whether antenatal intervention was provided.

Outcome

The main outcomes of this systematic review and meta-analyses will be to produce estimates of coinfection prevalence, risk factors for coinfection, and the risk of adverse pregnancy outcomes among women with coinfection. Specifically, in relation to each objective:

1. Prevalence of following combinations of coinfections:
   a. Malaria and syphilis.
   b. Malaria and gonorrhoea.
   c. Malaria and chlamydia.
   d. Malaria and trichomoniasis.
   e. Malaria and bacterial vaginosis.
   f. Malaria and *M. genitalium* infection.
   g. Malaria and at least one of the above curable STI/RTI.
2. Risk factors for coinfections combinations as defined above.
3. Risk of any adverse pregnancy outcome (miscarriage, stillbirth, preterm delivery, LBW, small for gestational age) among women with a coinfection, as defined above, compared with women with just malaria or just curable STI/RTI or neither malaria nor any curable STI/RTI.

Search strategy

Studies published from 2000 onward will be identified using three electronic databases: PubMed (NCBI interface, 1950 onwards), EMBASE Classic+EMBASE (Ovid interface, 1947 onwards) and Malaria in Pregnancy (MiP) Library.[22] The MiP Library is a free and comprehensive bibliographic database of literature on malaria in pregnancy compiled via systematic search of over 40 sources, updated every 4 months by the Malaria in Pregnancy Consortium,[23] and is currently hosted on the WorldWide Antimalarial Resistance Network website.[24] We will search PubMed and EMBASE using concept themes (1) pregnancy (pregnant, antenatal, prenatal), (2) malaria (plasmodium), (3) STIs/RTIs (sexually transmitted disease, genital tract infection, *Treponema pallidum*, syphilis, *Neisseria gonorrhoeae*, gonorrhoea, gonorrhoea, *Chlamydia trachomatis*, chlamydia, *Trichomonas vaginalis*, trichomoniasis, bacterial vaginosis, *M. genitalium*) and (4) sub-Saharan Africa (the name of each sub-Saharan country will be used individually). We will have no language restrictions. The full search strategies for all databases are available in online supplemental file 1. We will search databases in the second quarter of 2023 and repeat the search prior to completion of our analyses.

Screening

We will use Rayyan software to manage the results of all searches and facilitate the screening process.[25] All titles and/or abstracts of studies retrieved using the search strategy will be screened by the first two authors to identify studies that potentially meet the inclusion and exclusion criteria. Of the studies identified for initial screening, the full text will also be assessed for eligibility by two authors. The inclusion/exclusion status and rationale will be recorded for each study. If the two authors are unable to reach consensus regarding the inclusion or exclusion of any study, the last author will serve as an arbiter.

Data extraction (selection and coding)

We will extract study-level data onto a standardised form that will be used to create an electronic database. This will include study reference information, author(s), year of publication, study design, study duration and year(s) as well as following information for each objective:

Objective 1

Outcome measures of the number of pregnant women tested for malaria and/or curable STIs/RTIs, the number of pregnant women positive for those tests, diagnostic method(s) used, treatment type(s) and dosing frequency, and proportion of participants who were primigravidae, secundigravidae, multigravidae.

Objective 2

All possible risk factors will be recorded across eligible studies. For each risk factor, descriptive data (eg, mean and SD) or inferential statistical analyses (eg, ORs) will be extracted.

Objective 3

Prevalence of adverse pregnancy outcome will be recorded for each of the four categories of women: those who had only malaria, only curable STIs/RTIs, coinfection or neither malaria nor curable STIs/RTIs. If these number are not reported but risk ratio for adverse pregnancy outcome among coinfected women relative to each other infection category are reported, we will record the data.

Separately, we will obtain raster data of malaria parasite rate from the Malaria Atlas Project (MAP),[26] which will be representative of *Plasmodium falciparum* prevalence

among children 2–10 years of age[27 28] during the midpoint of each included study. Based on the MAP parasite rate estimate, transmission intensity will be categorised. We will contact authors of all eligible studies and ask for individual participant data.

Methodological quality assessments

Two authors will assess the quality of included studies using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system.[29] GRADE guidelines for a test accuracy addresses four domains: patient selection, index test, reference standard, flow and timing, which are derived from QUADAS-2 (Quality Assessment tool for. Diagnostic Accuracy Studies-2).[30] We will use a standard method for correcting diagnostic errors for all point prevalence data using the sensitivities and specificities of individual assays.[31] We will assess publication bias using funnel-plot assessment described by Sterne *et al*.[32]

Data synthesis

Study-level meta-analysis

For the study-level meta-analysis, the following methods will be used to address each of the objectives:

Objective 1

Pooled estimates of prevalence will be presented across multiple studies reporting the same coinfection combination (eg, malaria and syphilis).

Objective 2

All possible risk factors will be recorded across eligible studies and we will calculate pooled risk ratios for each risk factor.

Objective 3

We will calculate pooled prevalence of adverse outcomes by infection combination as well as pooled risk ratios of adverse pregnancy outcome among women with malaria and curable STIs/RTIs coinfection compared with women with only malaria or only curable STIs/RTIs or neither malaria nor any curable STI/RTI.

We will use risk ratios for binary outcomes and calculate 95% CIs and two-sided p values for each outcome. In studies where the effects of clustering may not have been accounted for, we will adjust the SD for the design effect.

Assessment of heterogeneity

The I^2 statistic will be used to assess between-study heterogeneity and will be interpreted using the guide from the Cochrane handbook[33]: might not be important (I^2=0%–40%), may be moderate (I^2=30%–60%), may be substantial (I^2=50%–90%) or considerable (I^2=75%–100%).

Individual participant data meta-analysis

Objective 1

Point prevalence estimates of the coinfection of malaria and STIs/RTIs will be calculated for each study along with 95% CI using Stata/IC V.16 software. Forest plots will be produced to display individual study point estimates and 95% CIs, as well as pooled prevalence estimates and 95% CIs for malaria and each STI/RTI across regions of sub-Saharan Africa.

Objective 2

We will use mixed effects regression methods to estimate the risk ratios for the effect of risk factors (eg, age, parity) on coinfection prevalence of malaria and curable STIs/RTIs, allowing for random effects across studies. Appropriate adjustment for clustering will be made for individual-level observations.

Objective 3

Same method (mixed effects regression) will be used to estimate the risk ratio of adverse pregnancy outcome among women with malaria and curable STIs/RTIs coinfection relative to women with only malaria or only curable STIs/RTIs or neither malaria nor any curable STI/RTI.

Subgroup analysis

We will undertake subgroup analyses in the individual participant data meta-analysis based on gravidity, malaria transmission intensity (MAP data), intervention type and frequency of administration. We will produce forest plots of pooled estimates of coinfection of malaria and STIs/RTIs. We will examine the correlation of malaria prevalence in children aged 2–10 and malaria or coinfection prevalence among pregnant women.

Sensitivity analysis

The effects of small studies will be examined by visually inspecting funnel plots of effect size versus SE. When there are a small number of studies, we will perform sensitivity analyses by removing outliers.

Protocol amendments

Any amendments to the protocol will be documented on the International Prospective Register of Systematic Reviews and in the final manuscript.

Patient and public involvement

Patients and the public were not involved in the development of this protocol nor will be in the systematic review.

ETHICS AND DISSEMINATION

We obtained approval from the Observational Research Ethics Committee of the London School of Hygiene & Tropical Medicine (LSHTM Ethics Ref: 26167). Results of this study will be disseminated via peer-reviewed publication and presentation at scientific conferences.

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Contributors RMC conceptualised the study idea and SS designed the overall structure of manuscript and drafted the early version of the manuscript. GG-L, CO and CS made comprehensive reviews of the manuscript throughout the submission process. MM, EBC and DC gave comments on the manuscript. RMC made a final review of the manuscript. All authors edited the manuscript and approved the final version.

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