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Trends in comparative efficacy and safety of malaria control interventions for maternal and child health outcomes in Africa: a study protocol for a Bayesian network meta-regression exploring the effect of HIV and malaria endemicity spectrum

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ABSTRACT

Introduction Unprecedented global efforts to prevent malaria morbidity and mortality in sub-Saharan Africa have saved hundreds of thousands of lives across the continent in the last two decades. This study aims to determine how the comparative efficacy and safety of available malaria control interventions intended to improve maternal and child health outcomes have changed over time considering the varied epidemiological contexts on the continent.

Methods We will review all randomised controlled trials that investigated malaria control interventions in pregnant women in sub-Saharan Africa and were published between January 1980 and December 2018. We will subsequently use network meta-regression to estimate temporal trends in the relative and absolute efficacy and safety of Intermittent Preventive Treatments, Intermittent Screening and Treatments, Insecticide-treated bed nets, and their combinations, and predict their ranking according to their relative and absolute efficacy and safety over time. Our outcomes will include 12 maternal and 7 child mortality and morbidity outcomes, known to be associated with either malaria infection or control. We will use intention-to-treat analysis to derive our estimates and meta-regression to estimate temporal trends and the effect modification by HIV infection, malaria endemicity and *Plasmodium falciparum* resistance to sulfadoxine–pyrimethamine, while adjusting for multiple potential confounders via propensity score calibration.

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Strengths and limitations of this study

- The use of multiple treatment comparisons will help generate a global estimate of comparative efficacy and safety of each malaria control intervention for each of the proposed study outcomes by combining direct and indirect evidence that will allow the comparison of interventions that have not previously been compared.
- We will apply propensity score calibration to adjust our estimates for population-level covariates, including population-weighted *Plasmodium falciparum* parasite rate, parasite resistance to sulfadoxine–pyrimethamine, and population-level prevalence of HIV, in addition to study-level covariates. This allows for improving the generalisability of our inferences while minimising bias due to confounders.
- This study has been registered in the International Prospective Register of Systematic Reviews.
- Data on the proposed epidemiological and clinical variables might be unavailable for some trial sites regarding adverse events, in which case we will consult non-randomised trials to preserve the precision of our inferences when deemed necessary.
- The inclusion of non-randomised trials, while helpful to maximise real-world applicability and the precision of our findings, may introduce bias in our inferences on adverse events.

BACKGROUND

Rationale

Despite the massive and unprecedented efforts by the international community over the last two decades to control and eliminate malaria, it continues to exert a huge burden on economies, health systems and communities in sub-Saharan Africa (SSA), in the era of Sustainable Development Goals.[1–3] Recent estimates by the Global Burden of Disease (GBD) 2016 study show that malaria remains the single most important cause of both mortality and morbidity across the continent, accounting for 10% of total disability-adjusted life years (DALYs) in all ages and both sexes, representing 11% among females and 18% in children under-5 years old.[3] This is notwithstanding the 52% reduction in DALYs attributable to malaria from 1990 to 2016, owing to important progress in disease control by global initiatives based on insecticide-treated bed nets (ITN), artemisinin-based combinations (ACT) and indoor residual spraying (IRS)[1 2]; as well as intermittent preventive treatments in pregnancy (IPTp) and health system strengthening measures.[4–6]

Bhatt *et al* provided a detailed description of the impact that ITN, ACT and IRS have had on the prevalence of *Plasmodium falciparum* infection and incidence of clinical malaria on the continent since 2000.[2] This comprehensive analysis, using data from field surveys, highlights that despite still being below the national and international targets, these interventions jointly prevented 60% of cases of clinical malaria, with ITNs being the intervention that contributed the most. In addition to reducing malaria cases, these interventions have also averted approximately 37% of malaria deaths across the continent during the period from 1990 to 2015, as illustrated by Gething *et al*.[1] The evidence provided by these studies is of considerable practical value in malaria control in SSA and shows that global efforts to control malaria on the continent have had successes. Specifically, the estimates on the proportional contributions of these interventions on malaria prevalence and mortality provide unique insights about the performance of these interventions under the ordinary conditions of implementation across the continent. However, their reliance on data from verbal autopsies, household surveys and vital statistics, which are known to have important limitations in terms of accuracy and completeness,[7 8] means that these estimates cannot necessarily be used to draw conclusions concerning trends in the full protective efficacy and safety of these interventions.[9–11] Additionally, no study has so far comprehensively assessed the contribution of other strategies also important for malaria control across the continent, such as IPTp, intermittent screening and treatments in pregnancy (ISTp), intermittent preventive treatments for infants (IPTi) or their combinations with ITN, IRS and ACT, while accounting for the varied epidemiological contexts across the continent.[12–16] These have however been shown to be particularly important for disease control and mortality prevention in populations who are most at risk of malaria infection and related adverse outcomes, such as pregnant women, newborns and infants.[15–20]

To date, many randomised controlled trials (RCT) have compared ITN with other interventions. Some of these trials compared ITNs with either IPTp or ISTp, while others have compared IPTp, ISTp and IPTi regimes with each other or with combinations of IPTp or ISTp and ITNs. Most of these RCTs have suggested that a combination of ITN and IPTp with sulfadoxine and pyrimethamine (SP) is more efficacious and safer than either intervention alone. However, the current emergence of *P. falciparum* resistance to SP, reported to range up to 100% across the continent,[21–26] shows that alternative interventions may be needed. ISTp with dihydroartemisinin–piperaquine as well as IPTp with SP–azithromycin have been shown to be efficacious and safe in recent trials.[15 18 20 22 27–29] Moreover, even in settings where resistance to SP is negligible, it is still unclear how many doses of IPTp(SP) are more efficacious and safe than any alternative regime.[17 19] This shows that a study that simultaneously compares all available malaria control interventions and ranks them according to their relative and absolute efficacy and safety to prevent maternal mortality and improve birth outcomes and child survival in SSA is needed.

For the first time, we will systematically review all RCTs that investigated malaria control interventions in pregnant women in SSA and subsequently use both direct and indirect evidence from eligible trials to simultaneously compare all interventions relevant for malaria prevention in pregnancy on the continent. For adverse events, we will include non-randomised trials in our network of evidence when the number of RCT available is not sufficient.[30] A multiple treatment comparison (MTC) approach within a Bayesian environment will be employed to jointly analyse individual patient data and make inferences on relative and absolute efficacy and safety of interventions. A comprehensive description of the MTC approach can be found in Mills *et al*.[31] Our method will allow us to generate a clinically relevant hierarchy of all malaria control interventions according to their relative and absolute performance in terms of efficacy and safety to prevent malaria mortality and morbidity in children and pregnant women. We will also be able to predict how this hierarchy has changed over time. To ensure the validity of our findings for the varied temporal and epidemiological settings on the continent, we will estimate time trends and the effect modification by HIV infection, malaria endemicity and *P. falciparum* resistance to SP. Despite being known to affect malaria control interventions, their impact on efficacy and safety of malaria control interventions in pregnancy and childhood has not been quantified so far.[22 32–34] We will control for potential bias due to heterogeneity in covariate distribution by adjusting our estimates to multiple potential confounders via propensity score calibration.

Objectives

We, therefore, aim to comprehensively and systematically estimate temporal and geographical trends in comparative efficacy and safety of malaria control interventions intended to improve maternal and child health outcomes in Africa. Specifically, our objectives are as follows: (1) to compare the protective efficacy and safety of malaria control interventions for maternal and child health outcomes, and (2) to estimate temporal trends and the effect modification by HIV infection, malaria endemicity, and *P. falciparum* resistance to SP in the efficacy and safety of malaria control interventions for maternal and child health outcomes.

METHODS

Search strategy and study selection

We will consider all peer-reviewed, published RCTs that compared the efficacy and/or safety of any relevant regime of IPTp, ISTp and ITNs with each other or with placebo in pregnant women. In cases where the data from RCT are not sufficient to conduct quantitative synthesis for adverse events, we will consult non-randomised trials to preserve the precision of our estimates. Two investigators (FA and JS) will independently conduct the search for eligible trials in Medline, Medline In-Process, Cochrane Central Register of Controlled Trials, Embase, CINAHL, African Index Medicus and SciELO, as well as ClinicalTrials.gov and the Clinical Trial Register at the International Clinical Trials Registry Platform of the WHO for ongoing trials. We will additionally search for grey literature in regulatory body and drug manufacturers databases.[35] The search for evidence will take place between February 2018 and December 2018 and the algorithm that we will use for evidence search is provided in online supplementary table S1. We will consider any relevant evidence regardless of the language in which it was published.

Criteria for considering studies for the network of evidence

We will review trials involving pregnant women conducted in SSA, that reported at least one of our study outcomes (described below) and that compared the efficacy and/or safety of relevant malaria control interventions. A sizeable number of trials assessing the efficacy and safety of important malaria control interventions were conducted in the 1980s.[36–38] Therefore, we will include in our analysis trials published between January 1980 and December 2018. Only those trials with at least two of the interventions described below will be eligible. Given the potential benefits that may be garnered by including evidence from non-randomised trials in MTC[30] and the paucity of data on certain study outcomes, we will use data from non-randomised trials when the RCT available are not sufficient to draw inferences with a reasonable precision on adverse events. For efficacy outcomes however, only RCT will be included. We will exclude trials whose full text of the publication is not available.

Type of eligible interventions and classification of arms

This study will compare the efficacy and safety of interventions jointly randomisable for prevention of malaria infection in pregnancy. These include IPTp, ISTp, ITNs and their combinations. We will consider IPTp, ISTp and ITNs based on the medicines and compounds summarised in online supplementary table S2, or their combinations. When deemed clinically plausible, interventions with similar mechanism and/or comparable population-level baseline coverage of interventions that may influence the outcomes under study on malaria prevention in pregnancy or childhood will be combined to minimise the number of nodes and the complexity of the network and therefore prevent positivity violation.[39]

Outcomes and outcome measures

Despite the paucity of evidence on maternal and child health outcomes attributable to *P. falciparum* infection that can be applied to the diverse malaria endemicity of SSA, the results of a systematic analysis of the GBD 2016 highlight that on the continent neonatal disorders and malaria, along with neglected tropical diseases, rank second and third respectively among the most important causes of morbidity and mortality in children under 5 years old.[3 40] The GBD further estimated that in this region approximately 866 660 stillbirths occurred in 2015, the highest toll when compared with other regions of the world.[41 42] Other recent studies have shown that low birth weight associated with *P. falciparum* infection results each year in 100 000 infant deaths across the continent, and that overall, between 75 000 and 200 000 infant deaths each year in SSA are directly attributable to malaria infection.[43 44] It has also been suggested that effective prevention of malaria in pregnancy could result in the reduction of severe maternal anaemia, low birth weight and perinatal deaths by 38%, 43% and 27%, respectively.[43] Studies conducted in areas of low, seasonal or unstable malaria transmission have further indicated that 24% to 37% of maternal mortality, 13% to 20% of stillbirths, 7% of preterm deliveries, 6% to 15% of anaemia during pregnancy, 16% of low birth weight and 8% of fever during pregnancy are attributable to malaria infection in pregnancy.[42 45–51] Relatively less attention has however been devoted to exploring the burden of adverse effects of malaria control interventions on maternal and child health outcomes. Nevertheless, a growing number of RCTs have linked stillbirth as well as other adverse pregnancy outcomes, not only to malaria in pregnancy, but to control interventions administered in pregnancy as well.[15 52] Other adverse maternal and child outcomes that have also been associated with either malaria or antimalarial interventions, including rashes and neonatal jaundice, while clinically meaningful, will not be assessed in the current analysis. Data on these outcomes are not routinely collected in RCTs.[18 20 53 54]

These figures highlight the large health and economic burden caused by malaria in pregnancy and childhood on the continent. We will therefore focus our effort to generate clinically meaningful hierarchies of malaria control interventions in pregnancy according to their relative and absolute efficacy and safety on maternal and child mortality and morbidity outcomes as listed in table 1.

Data extraction and quality assessment

Data on trial design and setting, individual patient characteristics and number of participants experiencing relevant events described above will be extracted from all eligible trials. Whenever deemed necessary, we will contact the authors of the eligible trials and experts for clarification and/or additional data. When available we will use data from previous Cochrane Reviews. In the case that the original authors are not responsive to our

Table 1 Outcomes and outcome measures

Item	Maternal outcomes	Child outcomes
1	Proportion of maternal deaths	Proportion of neonatal deaths
2	Proportion of maternal anaemia at delivery	Proportion of post neonatal deaths
3	Proportion of maternal peripheral malaria infection at delivery	Proportion of perinatal deaths
4	Proportion of anaemia in pregnancy	Proportion of infant deaths
5	Proportion of parasitaemia in pregnancy	Proportion of neonates with low birth weight
6	Proportion of severe anaemia in pregnancy	Proportion of neonates with congenital malaria infection
7	Proportion of spontaneous abortion	Proportion of neonates with congenital abnormalities at birth
8	Proportion of clinical malaria in pregnancy	
9	Proportion of premature delivery	
10	Proportion of severe maternal anaemia at delivery	
11	Proportion of placental malaria infection	
12	Proportion of stillbirth	

request, and Cochrane Reviews do not have relevant individual patient data, we will exclude these trials from our quantitative evidence synthesis. To account for population-level factors and thus maximise the generalisability of our findings to the ordinary conditions of implementation across the continent, we will also collect population-level data from non-randomised trials.[8 55 56] The evidence base will be graphically summarised by means of network plots where each intervention is shown by a node and randomised comparisons between interventions and/or medicines are shown by links between the nodes.[57] Two investigators (FA and JS) will conduct independent data extraction, risk of bias assessment using the Cochrane Collaboration tool[58] and subsequent scoring of eligible trials according to their propensity to the bias.[59] Further, to account our inferences on adverse events for heterogeneity in study design by combining data from RCT with those from non-randomised trials, we will include in our analysis an indicator variable reflecting whether the study is an RCT or a non-randomised trial. We will make use of comparison-adjusted funnel plots to visually assess the presence of small-study effects across the network of interventions.[60]

Baseline risk and transitivity assumption

The validity of our findings relies, among other considerations,[31] on the assumption that the interventions included in our network of evidence are jointly randomisable to prevent malaria infection in pregnancy and improve birth outcomes and child survival. We will assess our transitivity assumption by comparing the distribution of each of our covariates across the different pairwise comparisons in our network. To improve clinical plausibility of our transitivity assumption, we will adjust our estimates for confounders, including demographic characteristics, HIV infection, *P. falciparum* resistance to SP and baseline parasitemia. This will be accomplished using both study and population-level data, by means of meta-regression, if sufficient numbers of trials are available. Population-level data on malaria endemicity will be obtained from Malaria Atlas Project (MAP) databases.[2] Joint United Nations Programme on HIV/AIDS (UNAIDS) databases will be used to obtain data on HIV. These confounders and the variables reflecting the trial propensity to bias and the study design will be summarised into a propensity score, thus balancing the covariate distribution and collapsing multiple, potential confounding variables down to a single dimension.[61–64] For each outcome, we will separately analyse the effect modification by HIV infection, malaria endemicity and *P. falciparum* resistance to SP on the comparative efficacy and safety of interventions. This will allow us to estimate time-trends in treatment comparisons and assess the variation of the efficacy and safety of these interventions due to malaria endemicity, HIV and *P. falciparum* resistance to SP, while adjusting for imbalance in covariate distribution across trials and populations by means of propensity score calibration.[63 65 66] The inclusion of population-level data as covariates in our modelling framework will help maximise the applicability of our estimates to the ordinary conditions of implementation.[11 55 56] We will fit our network meta-regression model assuming common treatment by covariate interaction within treatment class.[67]

Patient and public involvement

The development of the research question and outcome measures was motivated by patients' and policy-makers' need for comprehensive evidence on clinical performance of malaria control interventions to improve maternal and child health outcomes, expressed in a format that they can easily understand, and that reflects local and current epidemiological realities and trends. The results will be disseminated to relevant communities and government agencies in national languages and through peer-reviewed publication and conference presentations.

STATISTICAL ANALYSIS

Inconsistency

Analysis of inconsistency in our network of evidence will be done using global and local methods. Assessment of inconsistency in the whole network will be conducted by means of Q statistic for inconsistency. Global I^2 will be derived via back calculation and used to determine the amount of between-trial heterogeneity which will be graphically explored using the tool developed by Krahn *et al*.[68] Each hotspot of inconsistency detected through this approach will be further analysed using per-comparison I^2 statistics and node splitting inconsistency p-values for each comparison.

Summary measures

We will use a Bayesian hierarchical framework based on binomial likelihood and random effects model to conduct our quantitative evidence synthesis and will report our posterior distribution of relative and absolute efficacy and safety estimates in odds ratios, number needed to treat and respective credible intervals. The quantitative synthesis of evidence will take place only when sufficient numbers of trials comparing interventions for a given study outcome are available in the literature. A detailed description of hierarchical modelling of MTC can be found elsewhere.[69–71] The ranking of treatments will be estimated probabilistically using surface under the cumulative ranking curve, which measures the extent to which a treatment is efficacious and safe relative to an ideal treatment that is invariably deemed to be the best without uncertainty. We will employ intention-to-treat (ITT) analysis for parameter estimation. ITT acknowledges that non-compliance and protocol deviations occur in actual clinical practice.[72 73] The use of ITT will therefore help us avoid overoptimistic estimation of the clinical performance of the interventions resulting from the exclusion of non-compliers, and maximise the applicability of our findings to the ordinary conditions of implementation.[72 74 75] Convergence of Markov chain Monte Carlo output will be assessed by means of effective sample size per transition and split $\hat{R}$ statistic.[76] We will use the Grading of Recommendations Assessment, Development and Evaluation framework for MTC to assess the overall feasibility of our inferences and follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses for network meta-analyses to report our findings.[57 77 78]

Sensitivity analysis

We will conduct sensitivity analysis to explore the impact of removing arms, combining interventions with similar clinical mechanisms and/or therapeutic effects, excluding interventions and/or designs that create inconsistency and/or small-study effects in our network and excluding trials with extreme doses and/or covariate values. Trials perceived to be of lower quality will be removed and the analysis will be repeated. Further, we will conduct sensitivity analysis to see the effect of performing quantitative evidence synthesis using the data from RCT and non-randomised trials as opposed to using only data from RCT. Additionally, we will check the effect of including the data from the grey literature in our network meta-analysis. Our decision as to which outcomes to include in our sensitivity analysis will be informed by the exploratory data analysis.[79] Sensitivity analysis will also be used for model selection between those models with vague priors and those based on empirical priors for heterogeneity parameters suggested by Turner *et al*.[80 81] Model performance will be assessed by means of leave-one-out cross-validation and the widely applicable information criterion.[76 82]

Statistical packages

This study will use Stata 15.0, Stan 2.18, and R 3.5 for all statistical analyses (StataCorp, 15 edn, 2017).[83 84] Exploratory classical meta-regression for the trials with the same design in our data set to obtain direct relative treatment effects, as well as assessment of small-study effects in our network of interventions will be done in Stata 15.0. We will fit our explanatory MTC models and derive our absolute and relative summary measures in Stan 2.18. Analysis of inconsistency, graphical visualisation of our findings and sensitivity analysis will be performed in R 3.5. The analysis of HIV infection, resistance of *P. falciparum* to SP and baseline parasitemia distributions and imbalances among our study populations will be conducted in a three-dimensional graphical environment using the 3D evidence network plot system developed by Batson *et al*.[85] This software will help assess the feasibility of our methods and the validity of our estimates.

DISCUSSION

In this analysis, we seek to explore temporal and geographical variations in the efficacy and safety of interventions suitable for malaria prevention in pregnancy. For the first time, our study will help understand how the absolute and relative efficacy and safety of these interventions to improve maternal and child health outcomes in SSA have changed over time, and how malaria endemicity, HIV prevalence and *P. falciparum* resistance to SP influence the clinical performance of these interventions across the continent, while adjusting for multiple potential confounders via propensity score calibration. Our findings and recommendations will be of unique practical value for policy-making and malaria control across the continent.

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Contributors FA conceived of and designed the research and drafted the protocol. He will conduct the literature search, extract data, conduct statistical analysis, draft the manuscript, draft the supplementary material of the manuscript, discuss the results and contribute to the revision of the final manuscript. TDM, AM and SN reviewed the protocol, will review the manuscript, support interpretation and policy contextualisation, discuss the results and contribute to the revision of the final manuscript. JS reviewed the protocol, will conduct the literature search, extract

data, review the manuscript, support interpretation and policy contextualisation, discuss the results and contribute to the revision of the final manuscript. BL reviewed the protocol, will support statistical analysis, review the manuscript, support interpretation and policy contextualisation, discuss the results and contribute to the revision of the final manuscript. All authors read and approved the final manuscript.

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