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Progression from uncomplicated to severe malaria among children in settings receiving different malaria control interventions in sub-Saharan Africa: a systematic review protocol

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ABSTRACT

Background Different malaria control measures are deployed simultaneously in endemic settings globally, with varying impacts on malaria burden. In sub-Saharan Africa, which bears the greatest burden of malaria, evidence on the impact of implementing various control interventions on malaria immunity remains unknown. This systematic review seeks to collate evidence on the extent of progression from uncomplicated to severe malaria among populations in sub-Saharan Africa settings receiving concurrent deployment of various malaria control measures.

Methods The review will use a priori criteria contained in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. An experienced librarian (AAK) will independently search for articles from the following databases: PubMed, Web of Science, Embase, Scopus and Google Scholar. Boolean operators 'AND' and 'OR' will be used in the article search. Identified articles will be managed using EndNote. Article screening for inclusion and data extraction will be done in duplicate by two reviewers (EJO, and BM). Data extraction tools will be developed and customised in Excel. Data will be analysed using both narrative and quantitative synthesis. The level of heterogeneity between study outcomes will be measured using the I^2 statistic. Subgroup analysis will be conducted to explore heterogeneity and establish the impact of different control interventions on progression from uncomplicated to severe malaria. A full systematic review and meta-analysis is expected to be ready for dissemination by the end of December 2025.

Ethical consideration and dissemination of findings This study did not involve human participants and so ethical approval was not sought. A full review and a meta-analysis will be published in a peer-reviewed journal and presented at national and international conferences.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The four databases to be searched will provide sufficient literature for this review.
⇒ The data abstraction algorithm was developed by a team of experienced librarians.
⇒ We may not easily find studies assessing the impact of malaria vaccines because they were recently rolled out in many African countries.
⇒ The study will be limited to children, and so it will be difficult to generalise the findings to the overall population.
⇒ Search will be limited to only publications in English, thus potentially excluding relevant articles in other languages.

INTRODUCTION

The major biological vector and parasite control measures with mass-scale application are Indoor Residual Spraying (IRS), Insecticide-Treated Nets (ITNs) and Intermittent Preventive Therapy (IPT).[1] All three interventions have significant coverage and utilisation across Africa. About 26% (12/45) of countries in sub-Saharan Africa deployed IRS in 1997, a figure that eventually increased up to 63% (29/46) by the end of 2017. The highest IRS coverage attained between 2010 and 2013 was due to the initiation of the intervention in West African countries.[2] Bertozzi-Villa *et al*[3] reported a plateau in ITN coverage in 2016 after over a decade of steady increase. Between 2018 and 2019, the continental-level matrix equally declined ever since mass ITN distribution started, decreasing from 360 million in 2017 to 337 million in 2017.[3] A study conducted in four countries across Africa reported a limited coverage of IPT in pregnancy, with less than a quarter of women eligible for treatment with the prophylaxis receiving at least three doses, making the continental coverage far below the universal coverage.[4]

The combination of ITNs and IRS for malaria mosquito vector control has become a common practice in Africa. The latest World Malaria report indicated that more than 25 countries had policies involving co-deployment of IRS and ITNs, with South Africa promoting IRS over ITNs, while 15 other countries preferred ITNs over IRS.[5] The two interventions are simultaneously deployed in selected households and communities in almost all these countries. A typical example is the mass application of IRS during epidemics in settings where bed nets had already been deployed.[6] In endemic countries, deciding what interventions should be applied in a particular setting depends on the associated financial cost and the availability of a storage and distribution system. In Zambia, ITNs are primarily deployed in rural areas, while IRS are deployed in urban and peri-urban settings because of high population density that can yield the most impact.[7]

Many studies have reported varied outcomes on the effectiveness of the combination of multiple malaria control interventions on disease incidence and prevalence. A 4-year prospective study that evaluated the National Malaria Control Programme in Eritrea found no added advantage of using IRS and ITNs as opposed to using either method alone.[8] The authors argued that the reason could be that the mosquito vector in circulation was endophilic, leading to the interventions' redundancy because both target indoor feeding vectors. A retrospective study conducted on control operations in the Solomon Islands reported a reduction in malaria and fever incidences in households with Dichlorodiphenyltrichloroethane (DDT), ITNs and health education. In Burundi, a co-deployment of IRS and long-lasting insecticide-treated nets (LLINs) led to a reduction in the indoor mosquito density but did not lead to an overall reduction in malaria transmission relative to the circulating intensity at the time. One systematic review reported that 5 out of 8 studies found that settings with both IRS and bed nets were more protected from malaria infections compared with those from IRS settings alone.[9]

Despite the approach of multiple deployments of interventions, sub-Saharan Africa still accounts for 95% of the global severe malaria and mortality burden.[10] The severe malaria burden among children is as high as 40.1% in certain parts of Northern Uganda, and it has had simultaneous deployment of IRS and LLINs for over a decade now.[11] Severe malaria burden in Africa varies from country to country and ranges from 10% to 70% of the total hospital child admissions.[12] Many studies have noted a drastic reduction in severe malaria cases during and shortly after the intervention application. A few months after this, cases of severity and death quickly rose above the routine average.[13] These interventions could have an indirect effect on the acquisition of naturally protective immunity, which is achieved after priming the immune system through exposure to multiple parasite strains. Children infected with a parasite strain to which their immunity has never been exposed have an increased likelihood of progression to severe diseases.[14] The more interventions there are, the less exposure to infections and the higher the chance of progression to severe disease. A systematic review by Snow and Marsh *et al*[15] reported that interventions that reduce exposure to infectious bites, such as ITNs and bed nets, lower malaria transmission but increase susceptibility to severe disease across all age categories. The information on the extent of progression from mild to severe malaria in settings receiving different control interventions in sub-Saharan Africa is unknown.

Rationale of the review

Despite reports on the reduction of new infections, cases of severe malaria have consistently remained high across disease-endemic regions of sub-Saharan Africa. With the presence of control interventions, coupled with longer periods of deployment, many children are protected either from infectious bites of mosquitoes or from low-level parasitaemia required to sustain some level of protective immunity. Exposure to mosquito vectors and new infections is expected to further reduce with the simultaneous deployment of multiple interventions and the introduction of vaccines. The need to deploy one or more interventions is driven by multiple factors, including variability in transmission patterns across different geographical areas. High transmission may require blocking transmission at a vector level and the human host level, necessitating more than one intervention. Low and seasonal transmission may require deployment of only a single intervention at a time. The inconsistency in the deployment interval of these interventions creates a window for vector multiplication and a new transmission cycle. This lack of exposure is expected to affect the development of natural immunity to clinical malaria. Consequently, more children (and even adults) are projected to progress to severe disease and death once they acquire infections from the new transmission wave. With different patterns of deployment of control intervention, we are not sure how it is impacting the acquisition of protective immunity. This systematic review will determine the prevalence of progression from mild to severe malaria in settings receiving different control interventions in sub-Saharan Africa.

METHODS

The review will be conducted following a priori criteria developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols guidelines.[16]

Review question

Primary review question

What is the prevalence of progression from uncomplicated to severe malaria among children in settings deploying multiple malaria control interventions in sub-Saharan Africa?

Table 1 The PICOS elements of the review question(s)

Element/criteria	Description	Search terms
P: population	Children in settings receiving different malaria control interventions in sub-Saharan Africa	► Children<5 years, Children, Children 6 to 17 years, infants, neonates, newborn, sub-Saharan Africa.
I/E: exposure	► Use of IRS in malaria mosquito vector control. ► Use of bed nets in malaria mosquito vector control. ► Use of vaccines for malaria control. ► Use of IPT for malaria parasite control. ► Use of a combination of IRS bed nets, vaccines and IPTs in malaria control.	► Bed nets, Insecticide Treated Nets, ITNS, Long Lasting Insecticide Treated Nets, LLINs Indoor Residual Spray, IRS, Chemoprevention, Mass drug administration, MDA, seasonal malaria chemo prevention, Larvicidal chemicals, Intermittent Preventive Therapy, IPT, Intermittent preventive treatment in pregnancy IPTp, Intermittent preventive treatment in infants IPTi, Intermittent preventive treatment in school-aged children IPTsc.
C: comparator	None	
O: outcome	*Primary outcome* Progression from mild to severe malaria	► Mild malaria, severe malaria, un-complicated, complicated malaria. ► simple malaria, complex malaria, cerebral malaria, malaria.
	Secondary outcome(s) Prevalence of subclinical parasitaemia	► Prevalence, proportion, frequency, trends. ► Parasitaemia, parasite load, asymptomatic malaria, sub-clinical parasitaemia.
	Trends in the levels of circulating IgG antibodies	Total IgG, IgG1, IgG2, IgG3, IgG4.
	Utilisation of malaria control interventions	► Length /time of application of the control intervention. ► Extent of utilisation/coverage of the control intervention (rural vs urban). ► Pattern of deployment of the control intervention (Singular vs multiple).
Study designs	RCTs, quasi experimental designs, case-control studies, cross-sectional studies, cohort studies (retrospective and prospective)	Before and after studies, Time series, Randomized control trials (RCTs), quasi experimental designs, case-control studies, cross-sectional studies, cohort studies
Time frame	2000 to date	2000 to date

IPT, intermittent preventive therapy; IRS, indoor residual spraying; PICOS, population, intervention/exposure, comparator, outcome and setting; RCT, randomised control trial.

Secondary review questions

1. What is the prevalence of subclinical parasitaemia among children in settings deploying multiple malaria control interventions in sub-Saharan Africa?
2. What are the trends in the levels of circulating Immunoglobulin G(IgG) antibodies among children in settings deploying multiple malaria control interventions in sub-Saharan Africa?
3. What are the patterns of deployment of multiple interventions for malaria control in different settings in sub-Saharan Africa?

The review questions are aligned to the Population, Intervention/Exposure, Comparator, Outcome and Setting (PICOS) format (table 1).

Eligibility criteria

Inclusion criteria

Articles published in peer-reviewed journals from 2000 to date; those reporting on the prevalence of disease progression from mild to severe malaria; articles reporting on the prevalence of subclinical parasitaemia; those reporting on the pattern of deployment of various interventions for malaria and finally, citations where full text can be accessed.

Exclusion criteria

Articles reporting only on entomological indicators; those reporting results from mathematical and epidemiological models; and editorials, commentaries or letters to the editor.

Patient and public involvement

It is not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

Search strategy

Data sources

Articles will be obtained from databases, including Scopus, PubMed, Web of Science and Embase. The article search will also be done using Google Scholar. Reference lists of included articles (bibliography search) and published by authors/researchers in malaria vector control will also be searched.

Article search

An experienced librarian (AAK) will conduct the database searches. The article search string will be developed and optimised in PubMed. The search string will then be customised to different databases. The Boolean operators 'OR' and 'AND' will be used to combine different search terms in the search string. The bibliographies of the included articles will also be screened for potential articles. Authors of selected articles will also be contacted to provide additional information on their work.

Search terms

The following search terms will be used during database search for potential articles.

'Malaria' OR 'Parasitaemia' OR 'parasite load' OR 'asymptomatic malaria' OR 'sub-clinical parasitaemia' AND 'Bed nets' OR 'insecticide-treated nets' OR 'ITNs' OR 'long-lasting insecticide treated nets' OR 'LLINs' OR 'indoor residual spray*' OR 'IRS' OR 'chemoprevention' OR 'mass drug administration' OR 'MDA' OR 'seasonal malaria chemoprevention' OR 'Larvicidal chemicals' OR 'intermittent preventive' OR 'IPT' OR 'intermittent preventive treatment in pregnancy' OR 'IPTp' OR 'intermittent preventive treatment in infants' OR 'IPTi' OR 'intermittent preventive treatment in school-aged children' OR 'IPTsc' OR 'protective antibodies' OR 'cytophilic antibodies' OR 'IgG1' OR 'IgG3 serum concentration' OR 'concentrations of IgG' OR 'expression of IgG' AND ('Prevalence' OR 'proportion' OR 'frequency' OR 'trend*'). The search strategy has been attached separately as online supplemental file 2.

Planned search dates

From 3 August 2025 to 31 May 2026.

Article screening

Two independent reviewers (OJE and BM) will screen the articles using a preset criterion. The article screening tool will be developed and customised in Excel. The tool will be piloted on five articles and validated prior to use. The two reviewers will screen the titles and abstracts of all the articles for inclusion. Articles that are included in the title and abstract screening will then undergo full-text screening. Any disagreement between the two reviewers will be resolved through discussion and consensus. Any further disagreements will be resolved through a tiebreaker (MO).

Data abstraction

Data will be abstracted following the principles of PRISMA. EndNote will be used to manage articles. Data abstraction has been attached separately as online supplemental file 1.

Data items

The following items will be extracted from the published studies.

Details of the publication: title of the journal, author(s), year, region, country where the study was conducted and funding source.

Details of study participants: this includes information on mild malaria, severe malaria, cerebral malaria, malaria anaemia, malaria prevalence, parasite load, subclinical malaria and antibody level.

Details of interventions: this will include intervention type, length of deployment, patterns of deployment (singular vs multiple) and extent of utilisation/coverage.

Data management

Abstracted data will be stored in Excel V.2020. Articles for review will be kept in EndNote.

Interactions between variables: the effects of combinations of different malaria control interventions on progression from mild to severe malaria will also be collected, but as an additional variable.

Statistical analysis

Synthesis of data

This study will use a random-effects meta-analysis model because we expect heterogeneity among the studies that will be selected. This will also accommodate wider confidence intervals and larger p values for the final pool estimates. The meta-analysis result will be plotted in a forest plot.

Effect size measurement

Risk ratio and 95% CI will be calculated to process the dichotomous data, such as malaria test outcome, form of cerebral malaria and type of interventions. For continuous variables, such as antibody levels, parasite load and age, Weighted Mean Difference/Standard Mean Difference will be used.

Heterogeneity assessment

Quantitative data synthesis will be performed only in the event that there is no high heterogeneity in the main review outcomes of the selected articles. The I^2 statistics will be used to establish the level of heterogeneity in the articles. The percentage heterogeneity that can be attributed to the study variance can be indicated by the I^2. 25% indicates low heterogeneity, 50% indicates moderate heterogeneity, while 75% indicates high heterogeneity. Where required, subgroup analysis of included articles with high heterogeneity will be conducted. Establishing the source of heterogeneity will help determine populations that may be more sensitive to interventions and severe disease.

Risk of bias assessment

The expected Risk of Bias (RoB) includes performance bias, detection bias and publication/reporting bias. Symmetry of the plot and funnel plot will be used to detect the likelihood of publication bias among the articles included in the review. Trim and fill methods will be used to adjust for publication bias in the selected articles.

The ROBINS-1 tool will be used to assess the other risk of bias in the studies.

Study limitations

There might be more control in areas with higher disease burdens.

We may not easily find studies assessing the impact of malaria vaccines because they were recently rolled out in many African countries.

The study will be limited to children, and so it will be difficult to generalise findings to the overall population.

The search will be limited to publications in English, thus potentially excluding relevant articles in other languages.

The study will not collect data on mosquito vector resistance.

Ethical consideration and dissemination of findings

This study did not involve human participants, and so ethical approval was not sought. Full review and meta-analysis will be published in a peer-reviewed journal and presented at national and international conferences. A full systematic review and meta-analysis is expected to be ready for dissemination by the end of December 2025.

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REFERENCES

1 Li J, Docile HJ, Fisher D, *et al*. Current Status of Malaria Control and Elimination in Africa: Epidemiology, Diagnosis, Treatment, Progress and Challenges. *J Epidemiol Glob Health* 2024;14:561–79.
2 Tangena J-AA, Hendriks CMJ, Devine M, *et al*. Indoor residual spraying for malaria control in sub-Saharan Africa 1997 to 2017: an adjusted retrospective analysis. *Malar J* 2020;19:150.
3 Bertozzi-Villa A, Bever CA, Koenker H, *et al*. Maps and metrics of insecticide-treated net access, use, and nets-per-capita in Africa from 2000-2020. *Nat Commun* 2021;12:3589.
4 Pons-Duran C, Llach M, Sacoor C, *et al*. Coverage of intermittent preventive treatment of malaria in pregnancy in four sub-Saharan countries: findings from household surveys. *Int J Epidemiol* 2021;50:550–9.
5 Nalinya S, Musoke D, Deane K. Malaria prevention interventions beyond long-lasting insecticidal nets and indoor residual spraying in low- and middle-income countries: a scoping review. *Malar J* 2022;21:31.
6 Nash RK, Lambert B, N'Guessan R, *et al*. Systematic review of the entomological impact of insecticide-treated nets evaluated using experimental hut trials in Africa. *Curr Res Parasitol Vector Borne Dis* 2021;1:100047.
7 Munn Z, Stone JC, Barker TH, *et al*. Residual insecticide surface treatment for preventing malaria: a systematic review protocol. *Syst Rev* 2023;12:89.
8 Nyarango PM, Gebremeskel T, Mebrahtu G, *et al*. A steep decline of malaria morbidity and mortality trends in Eritrea between 2000 and 2004: the effect of combination of control methods. *Malar J* 2006;5:33.
9 Kleinschmidt I, Schwabe C, Shiva M, *et al*. Combining indoor residual spraying and insecticide-treated net interventions. *Am J Trop Med Hyg* 2009;81:519–24.
10 Oyegoke OO, Akoniyon OP, Ogunsakin RE, *et al*. A Systematic Review and Meta-Analysis of Malaria Test Positivity Outcomes and Programme Interventions in Low Transmission Settings in Southern Africa, 2000-2021. *Int J Environ Res Public Health* 2022;19:6776.
11 Ocen E, Opito R, Tegu C, *et al*. Severe malaria burden, clinical spectrum and outcomes at Apac district hospital, Uganda: a retrospective study of routine health facility-based data. *Malar J* 2023;22:325.
12 Camponovo F, Bever CA, Galactionova K, *et al*. Incidence and admission rates for severe malaria and their impact on mortality in Africa. *Malar J* 2017;16:1.
13 Kané F, Keïta M, Traoré B, *et al*. Performance of IRS on malaria prevalence and incidence using pirimiphos-methyl in the context of pyrethroid resistance in Koulikoro region, Mali. *Malar J* 2020;19:286.
14 Stanisic DI, Mueller I, Betuela I, *et al*. Robert Koch redux: malaria immunology in Papua New Guinea. *Parasite Immunol* 2010;32:623–32.
15 Snow RW, Marsh K. The consequences of reducing transmission of Plasmodium falciparum in Africa. *Adv Parasitol* 2002;52:235–64.
16 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.