The effects of childhood exposure to malaria on cognition and behavior: A systematic review protocol

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Protocol

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Abstract

Background: Malaria is one of the major contributing risk factor for poor development of children living in low- and middle- income countries (LMICs). However, little is known about the specific domains of cognition and behavior that are impacted by malaria, the extent of these deficits, and the severity of malaria infection that is associated with these deficits. The objective of this review is to determine the effect of malaria infection on cognition and behavior among children living in LMICs.

Methods and analysis: We will systematically search online bibliographic databases including PubMed, EMBASE, Cochrane Collaborative Database, CINAHL and PsycINFO as well as Google Scholar and bibliographies of pertinent articles. We will include studies with a comparison group (e.g., clinical trials, cohort, cross-sectional and case–control studies) involving children under 18 years of age living in LMICs, as determined by World Bank Criteria, with either an active malaria infection or history of malaria. Included articles must also measure cognitive and behavioral outcomes using standardized instruments. Studies will be excluded if they are not in English, lack a control group, take place in a high-income country, or if a standardized instrument was not used.

Two reviewers will independently review all articles to determine if they meet eligibility criteria. Any conflicts will be resolved after discussion with a third reviewer. When a list of included articles is finalized, two reviewers will extract data to populate and then cross check within an electronic table. Risk of bias and the strength of evidence and recommendations will be assessed independently using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, and a final score will be given upon consensus. For sufficiently homogeneous data on measured outcomes in multiple studies, we will investigate the possibility of pooling data to perform a meta-analysis.

Discussion: This systematic review will evaluate the evidence of the effect of malaria on the cognitive and behavioral outcomes. Findings from this planned review will generate insight on the domains affected by the different forms malaria infection and may inform subsequent malaria interventions and future research in pediatric care.

Background

Malaria remains a public global health challenge that disproportionally affects children who already face multiple other risk factors for growth and development, such as poverty and malnutrition. Between 300–600 million people suffer from malaria each year, and 90% of these cases occur in young children in sub-Saharan Africa (1). Over 300,000 of children infected with malaria will die of the disease (2, 3). Those who survive often suffer multiple morbidities, including increased risks of neurological, cognitive and behavioral deficits (4–8). With the prevalence of malaria infection worldwide, vast numbers of children are at increased risk of cognitive and behavioral impairments. By not reaching their full developmental potential, these children are estimated to have a 20% deficit in their adult incomes, which affects families, communities, and countries (9).

Only one review has evaluated the effects of *Plasmodium falciparum* on cognition, which found potential deficits in attention, memory, visuospatial skills, language, and executive functions after malaria infection (6). While this review brought attention to this critical issue, it was published over ten years ago and lacks differentiation regarding severity or different forms of malaria infection. A knowledge gap currently exists regarding what specific domains of cognition and behavior may be negatively impacted by malaria infection and the extent of that impact. Furthermore, it is unclear how other potential factors, such as varying intensities of malaria infection, may impact cognition and behavior.

In recent years, cognitive and behavioral assessments are increasingly performed post-malaria infection, in both clinical and research settings. However, a succinct synthesis of these data has not been performed to describe the impact that various forms of malaria infection have on cognitive and behavioral outcomes in children, as well as other factors that may be contributing to cognitive and behavioral deficits in this population. This systematic review is necessary to help find, appraise and summarize the current evidence on malaria infection effects on cognitive and behavioral performance and may provide evidence to inform clinical care and highlighting further areas for investigation.

Objectives

The objective of this systematic review is to determine the effect of malaria infection on cognition and behavior among children living in low- and middle-income countries (LMICs). We will achieve this objective by addressing the following research questions:

a.) Which cognitive and behavioral domains are negatively impacted by malaria infection?

b.) To what extend are these domains impacted?

c.) Which forms of malaria are associated with specific deficits in cognition and behavior?

d.) What are other risk factors for cognitive and behavioral deficits?

Methods And Analysis

We developed our methods following the instructions of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines This systematic review will be also written in accordance with the PRISMA for systematic review protocols (PRISMA-P) statement (10, 11) (See additional file 1).

Eligibility criteria

Quantitative studies investigating the association between malaria and cognitive and behavioral outcomes will be included. Studies will be selected according to the following eligibility (inclusion/exclusion) criteria (Table 1; See additional file 2):

Inclusion criteria

Target population: Children below 18 years with malaria infection by laboratory diagnosis (i.e. microscopic diagnosis, molecular diagnosis, antigen detection, serology).

Setting: LMICs, as determined by World Bank Criteria

Primary outcome: cognitive and/or behavior score as determined by a psychological assessment.

Exclusion criteria

Studies repeating the cohort population reporting similar outcomes

Malaria infection determined by clinical diagnosis only (patient symptoms and on physical examination)

Human studies that do not assess cognitive and or behavioral function as an outcome

Animal studies

Studies without a control or comparison group

Non-English studies

Participants older than 18 years of age

Studies in high income countries or not within LMICs, as determined by World Bank Criteria.

We will exclude reviews, opinion pieces and letters to the editor, commentaries, abstracts and case series including <5 individuals.

Participants

The target population for inclusion is children (≤18 years) with active or recent malaria (within 12 months) infection. Inclusion of longitudinal studies will allow us to evaluate the potential impact of malaria on cognition and behavior over time (12).

Exposure/ target condition

We will include any active malaria infection or any recent malaria infection that has occurred within 12 months of the cognitive and behavioral assessments. When possible, we will classify the malaria according to the following definitions:

Asymptomatic malaria is a form of *Plasmodium* malaria infection that lacks typical clinical symptoms, but has submicroscopic parasite densities detectable by microscopy, rapid diagnostic test (RDTs) or molecular methods (13). Asymptomatic malaria is commonly a submicroscopic infection (does not necessarily produce gametocytes chiefly detectable by molecular methods than microscopy).

Uncomplicated malaria is a form of *Plasmodium* malaria infections that are accompanied by fever and/or other symptoms like nausea, vomiting, muscle aches, abdominal pains, chills and sweat that are indicative of malaria. These infections are, almost without exception, detectable by microscopy or rapid diagnostic test (13).

Severe malaria is almost exclusively caused by *Plasmodium falciparum* infection characterized by prostration, impaired consciousness, respiratory distress (acidotic breathing), multiple convulsions, circulatory collapse, pulmonary oedema (radiological), abnormal bleeding, jaundice, hemoglobinuria, severe anemia with quick progression to life- threatening disease (14, 15). However, *P. vivax* (13) and *P. knowlesi* (16, 17) can also cause severe disease.

If the specific form of malaria infection is not clear from the publication, it will be labeled as “general malaria infection.” If the study cohort contains individuals with different forms of malaria infection, it will be labeled as “mixed malaria infection.”

Outcome

We will include standardized methods of measuring cognition and behavior (questionnaire-based scales and or neurocognitive assessments). All instruments will be reviewed by a psychologist prior to final inclusion.

Timing

Our search will not be restricted by earlier publication date and length of follow-up in order to compare outcomes across time. We will include studies published until the time of the search is performed.

Note: Our preliminary scoping of the literature suggested no relevant citations would be retrieved prior to 1920.

Setting

Only studies undertaken in low- and middle- income countries will be eligible for inclusion, due to the high burden and receptivity of malaria infection in these settings. Income classification of countries will be according to the World Bank criteria (18).

Language

Studies published in English language and available in full text will be eligible for inclusion. Studies published in any language other than English will not be included. This criteria is due to the limited resources available in performing this review.

Information sources

We will systematically search MEDLINE (via PubMed), EMBASE, Cochrane Collaborative Database, CINAHL and PsycINFO. We will also search the reference lists of included studies to identify other studies. We consulted a medical librarian at Indiana University to develop our search strategy. Our final search terms include text words; malaria (asymptomatic, uncomplicated and severe), cognitive, behavior, child development; MESH terms for cognition, behavior, child, malaria with the child filter (birth–18 years) (see Supplement 1). We will also hand-search the bibliographies of relevant studies and review articles, as well as search Google Scholar for additional potentially eligible articles.

Study screening, selection and data extraction

Studies will be included only if they meet the full inclusion criteria above and not met any exclusion criteria. The abstracts and full-text articles retrieved using the search strategy will be imported into Endnote software and duplicates will be removed. Two of the authors will independently screen studies for inclusion at two levels a) title/abstract and b) full text based on the eligibility criteria. We will screen full text articles of studies that meet eligibility at title and abstract screening. For any discrepancies, another author will serve as a third rater to create a consensus. Three authors will extract data from the full text articles of the included studies using an Excel spreadsheet screening and data extraction form developed a priori to capture study details (e.g., authors, year, country, setting, length of follow-up); sample characteristics (e.g. age, gender, number of participants included), study design (e.g. Randomized Controlled Trials (RCTs), case control, cohort, cross-sectional), descriptions of how malaria, cognition and behavior are assessed (tests and cut-off values used), and study outcomes (Table 2; See additional file 2). The Excel spreadsheet and Endnote library will be used to manage records and data throughout the review.

Assessment of risk of bias and grading strength of evidence

To evaluate the methodological quality and strength of evidence on the topic, we will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (19, 20). Two raters will independently assess the strength of evidence in five areas: study design, quality, consistency, directness and precision. The raters will add or subtract points for each of these categories in line with GRADE guidelines. By adding or subtracting points, GRADE helps us assess whether further evidence from newly published studies would change the conclusions of the review. The raters will resolve discrepancies through consensus and involvement of a third rater.

Data synthesis and statistical analysis

We will narratively synthesize the extracted data from all included studies. For subsets of studies that are sufficiently homogeneous in terms of sample characteristics, measures of cognition and behavior, and methods (e.g., design, setting, length of follow-up), a meta-analysis will be considered, for which a biostatistician will be asked to join the review team. A PRISMA flow chart will be developed to show each level of the review process.

Discussion And Outcomes

The systematic review will provide meaningful insights on the effects of malaria on cognition and behavior of children, including the adverse effects of post-malaria survival. Additionally, the review will inform strategies for the prevention and management of malaria and guide further research in addressing the current gaps in knowledge regarding cognitive and behavioral outcomes associated with malaria episodes. The review findings will be presented at academic conferences and published in a peer reviewed journal.

This systematic review will be the first to examine a full range of both cognitive and behavioral outcomes in children in malaria-endemic and LMICs, as well as explore of various forms of malaria infection may impact outcomes. Findings from this review may support clinicians, health experts and policy makers develop guidelines to minimize deficits and impairment due to malaria infection for children surviving malaria.

Ethics and dissemination: We will not seek for ethical approval as this is a systematic review protocol. We will synthesize literature on the cognitive and behavioral outcomes of children surviving malaria. The findings of this review will be shared through peer-reviewed publications to provide information to scientists when developing guidelines for managing the outcomes in LMICs.

List Of Abbreviations

CM—Cerebral malaria

GRADE - Grading of Recommendations Assessment, Development and Evaluation

LMICs—Low and middle income countries

P. falciparum—Plasmodium falciparum

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis

RCTs—Randomised Controlled Trials

RDTs - Rapid diagnostic tests

SMA—Severe Malaria Anaemia

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

Not applicable

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

AS conceived the study, wrote the protocol and will lead the conduct of the systematic review. JN, SK and MM revised the protocol for important intellectual content. EW and MM will provide conceptual and methods guidance throughout the review. PB, NN, CJ will provide important intellectual content and subject specific guidance. All authors have read, provided critical revisions to the manuscript, and approved the final version of the submitted protocol.

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Not applicable

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Supplementary Files Legend

Supplement 1

Search strategy

("cognitive"[All Fields] AND (functions [All Fields] OR function [All Fields] OR functioning [All Fields])) OR (neurocognitive[All Fields] OR neurocognitively[All Fields] OR neurocognitives[All Fields] OR neurocognition[All Fields] OR "cognitive"[All Fields] OR cognitives[All Fields] OR cognitively[All Fields] OR "cognition"[MeSH Terms] OR "cognition"[MeSH Terms] OR "cognition"[All Fields] OR "cognition disorders"[MeSH Terms] OR ("cognition disorders"[MeSH Terms] OR ("cognition"[All Fields] AND "disorders"[All Fields])) OR "cognition disorders"[All Fields] OR "child development"[MeSH Terms] OR "child development"[Title/Abstract] OR "child behavior disorders"[MeSH Terms] OR "child behavior"[MeSH Terms]) AND ("malaria"[MeSH Terms] OR "malaria"[All Fields])

Embase

(('mental disease' OR 'cognition' OR 'behavior disorder' OR 'developmental disorder' OR 'child development' OR 'neurological disorder' OR 'neurodevelopment' OR 'executive function' OR 'language') AND ('malaria' OR '*falciparum*' OR 'remittent fever') OR 'malaria infection' OR '*plasmodium*')) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile2Tables1and2.docx
- Additionalfile1PRISMAPchecklist.docx