Resurgence of blackwater fever among children in sub-Saharan Africa: a scoping review protocol

George Paasi 1,2, Carolyne Ndila,2 Florence Alaroker,3 Julian Abeso,4 Glorias Asiimwe,5 Francis Okello,1 Peter Olupot-Olupot1,2

ABSTRACT
Introduction Blackwater fever (BWF), a complication of malaria, has in the past been considered as a rare complication of malaria in children living in high transmission settings. More recently, however, a growing number of paediatric clusters of BWF cases have been reported predominantly in sub-Saharan Africa (SSA). The aim of this study is to map evidence on BWF among children in SSA from 1 January 1960 to 31 December 2021.

Methods and analysis This review will be guided by Arksey and O’Malley’s methodological framework for scoping reviews with methodological refinements by Levac et al and will comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews’ guidelines. Five electronic databases (MEDLINE via PubMed, Embase, the Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Psychnfo) will be systematically searched using predefined keywords. In addition, reference lists of included articles will be searched. Our multidisciplinary team has formulated search strategies and two reviewers will independently complete study eligibility screening, final selection and data extraction. A third reviewer will adjudicate the final decision on disputed articles. Bibliographic data and abstract content will be collected and analysed using a data-charting tool developed iteratively by the research team.

Ethics and dissemination This scoping review being a secondary analysis does not require ethics approval. We anticipate results of this review will broaden understanding of paediatric BWF in SSA and identify its research gaps in SSA. We will be disseminating results through journals and conferences targeting primary care providers.

INTRODUCTION
Blackwater fever (BWF) is a clinical syndrome characterised by an acute intravascular haemolysis resulting in passing tea-coloured or cola cola urine.1,2 It is almost exclusive to Plasmodium falciparum malaria.3 The first description of BWF was from Africa by Easmon 1883, since then, the majority of subsequent reports (1885–1960) focused on case series in non-indigenous residents. Historically, the case definition included Caucasian who had lived or visited malaria endemic area for a long time (>3 months) without previous exposure to malaria and were taking quinine in inappropriate dose or schedule for malaria prophylaxis and/or treatment.4–6

At the turn of the 20th century, the aetiology of the syndrome was further described though the elucidations remain incomplete. The consensus view was that susceptibility to BWF resulted from interaction between host response to repeated P. falciparum malarial attacks5,7 and recurrent synthetic aryl amino alcohol antimalarials exposure8 such as quinine, mefloquine and halofantrine.9–12 Some studies on the relationship between glucose-6 phosphate dehydrogenase deficiency (G6PDd) as a trigger of BWF are ambivalent. For insistence, while G6PDd was previously reported to be associated with massive haemolysis among malaria patients who use quinine or other quinolone drugs for treatment of malaria,9,13 more recent descriptions in Eastern Uganda do not associate the...
phenomenon to G6PDd.\textsuperscript{14} Furthermore, the relationship between BWF and G6PDd has been reported to be geographically-specific owing to the more severe phenotypes of G6PDd variants in Mediterranean and Asian populations, compared with the milder African variant, which retains ~10\%–15\% activity and thus less susceptible to oxidant stress.\textsuperscript{15} BWF has been conventionally used to describe \textit{P. falciparum} malaria complicated by haemoglobinuria, however, recent studies by O’Donnell \textit{et al.}\textsuperscript{2} and Olupot-Olupot\textsuperscript{15} have reported two biologically different proteins in dark/coloured urine in severe malaria: haemoglobinuria and myoglobinuria, but with possible different pathophysiology. Haemoglobinuria, a marker of severe haemolysis, is mainly associated with acute intravascular haemolysis, while myoglobinuria manifests mainly among children with cerebral malaria and hyperlactataemia; suggesting hypoxic muscle cell injury from sequestration of parasitised red blood cells.\textsuperscript{2} This suggests a multiatiological and pathophysiology process and hence the condition according to the two researchers is a syndrome called dark urine syndrome.

BWF has in the past been regarded as a rare complication of malaria in children living in high transmission settings.\textsuperscript{16–18} More recently, however, a growing number of paediatric case series have been published from both Africa\textsuperscript{3} \textsuperscript{19–22} and Oceania.\textsuperscript{2} Some studies have described the syndrome of BWF in which they documented varying prevalence of 6\%–48\%\textsuperscript{23} 24 and 11\%–59\%\textsuperscript{25} 26 of patients with severe malaria, respectively. Evidence from the past three decades underscores the resurgence of BWF in children though these descriptions remain incomplete. Potential reasons for these trends are varied, but geographical localisation of BWF together with fewer research resources directed towards its epidemiology, pathophysiology and interventions may play a role.\textsuperscript{22 27} 28 While it is evident a number of studies have been conducted on BWF in children in sub-Saharan Africa (SSA), this information has hardly been collated and synthesised. Collating and synthesising these data is important for the broader understanding of the paediatric description of BWF with its associated morbidity and mortality in SSA. This will guide implementers on the ground, reveal research gaps and shape intervention and guidelines/policy developments aimed at improving outcomes of children with BWF in SSA. The main objective of this study is to map evidence on BWF in children in SSA from 1 January 1960 to 31 December 2021. This novel study will establish the direction for the researchers on BWF in children and discuss the future agenda.

**METHODS/DESIGN**

According to Arksey and O’Malley,\textsuperscript{29} the aim of a scoping review is to map rapidly the key concepts underscoring a research area and the main sources and types of evidence available. Though a relatively recent method of evidence synthesis especially in the health discipline, there has been growing number of studies since the development of the scoping review framework in 2005 by Arksey and O’Malley.\textsuperscript{29}

We will undertake a scoping review of published scientific literature on BWF in children in SSA as the preferred method of evidence synthesis to explore and map the resurgence of BWF in this population. This methodology is particularly important in comprehensively and systematically mapping the literature and identifying key concepts, theories, evidence or research gaps.\textsuperscript{30} The main strength of the scoping review method
as applied to our study is that it allows for analysis of a broader research question.31 This scoping review aims to collate published literature on BWF in children in SSA. We will aim to map the breadth of literature on BWF in children in SSA by categorising articles to provide a thematic analysis of their content.

**Review team**

This scoping review is being conducted by a team comprised of multiprofessional expert clinicians and academicians in the field of paediatric infectious diseases (PO-O, JA, FA and GP), an information scientist (GA), a methodologist (CN) and a research fellow (FO). Table 1 shows author involvement and timeline for study completion.

**Protocol design**

This review will follow the methodological steps outlined by Arksey and O’Malley29 with the methodological refinements proposed by Levac et al.32 This process includes the following five steps illustrated in figure 1.

We will also follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews: checklist and explanation33 (see online supplemental additional file 1). The population–concept–context (PCC) framework34 will also be used in this study to determine the eligibility criteria for potential articles to address the research question. This scoping review will be conducted from 1 March 2022 to 30 October 2022.

**Stage 1: identifying the research questions**

According to Arksey and O’Malley, the first stage in the process of conducting a scoping review is to identify the research question(s) for the study and to link the question with purpose of the study.29 32 Bearing that in mind, the team developed a series of research questions related to the aims of the study through an iterative process. Since in addition to iteration, the process of conducting a scoping review requires a reflexive approach to each stage as the team becomes increasingly familiar with the literature, there is a possibility that revisions may be made to the research questions. Six research questions were identified to guide the scoping review.

These questions were developed via a series of research team meetings:

1. What are the volume, year wise distribution and journal wise distribution of peer-reviewed published literature on BWF in children in SSA?
2. What are the trends in publications and citation of peer-reviewed published literature on BWF in children in SSA?
3. What is the aggregate prevalence of BWF in children in SSA?
4. What is the paediatric case description of BWF in SSA?
5. What are the leading thematic areas in childhood BWF in SSA, what are their composition and relationships among them?
6. What are the emerging topics in childhood BWF in the light of past research and current reports on the same in SSA?
Stage 2: identifying relevant studies
At this stage, the team methodically decided on the eligibility criteria, databases to search and formulated a search strategy with key terms. We developed a search strategy for relevant studies using the PCC framework as recommended by the Joanna Briggs Institute for scoping reviews.35

Eligibility criteria
The eligibility criteria were categorised according to the PCC framework.
Inclusion criteria:

Population
► Children.

Concept
► Research articles reporting on BWF in children in SSA carried out between 1 January 1960 and 31 December 2021 (1 January 1960 corresponds to the time when BWF become rare owing to quinine (which was a proven trigger of BWF) being increasing replaced by chloroquine.36 However, in the past three decades, there has been an increasing number of BWF reports published especially in SSA). The selected time range will enable exploration of the resurgence of BWF in this region.

Context
► Research articles are limited to SSA, a high malaria transmission region.37
► Original research articles (primary observational studies with cross-sectional or prospective research designs, case–control studies and studies with experimental designs shall be included.)
► Articles published in English.
► Full-text articles available for review.

Explicit exclusion criteria identified are
► Journal articles that are book reviews, opinion articles, review articles, commentaries or editorial reviews will be excluded.
► Studies not published in the English language will be excluded.

Databases
Peer-reviewed published articles on BWF in children in SSA will be searched from the following databases: MEDLINE via PubMed, EMBASE, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PsycINFO.

Search terms
The search terms used for this scoping review will follow the PCC model. The key terms to be used in the database search will be “blackwater fever,” “children,” and “sub Saharan Africa.”

Search strategy
The search strategy will follow the three-step process recommended by the Joanna Briggs Institute.35 An experienced university librarian (GA) will conduct article search. Medical Subject Heading will be used in article search. The unique terms will be combined using Boolean operators ‘OR’ or ‘AND’. The first of these steps has been undertaken and involved a limited preliminary search of one online database relevant to the topic (MEDLINE via PubMed (preliminary search done on 15 November 2021)). The pilot PubMed search string is attached as online supplemental additional file 2.

The second step will contain an analysis of the text words contained in the title and abstract of retrieved papers, and of index terms used to describe the articles. A second search using all identified keywords and index terms will then be undertaken across all included databases (EMBASE, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PsycINFO).

The third and final step will involve manually checking the reference lists of all included articles for additional relevant studies. The final included studies will be exported to Endnote reference management software and duplicates will be removed.

Stage 3: study selection
The endnote software will be used to deduplicates included articles. Study selection will be done in two phases. First, a single reviewer (GP) will screen the titles using a priori criteria. Studies will be labelled as ‘included,’ ‘exclude’ or ‘uncertain.’ For insistence, titles that indicate BWF in adults and studies on BWF outside SSA will be excluded. At this primary stage of the review, any uncertainty with a title will not exclude the article for consideration in the second phase of article screening.

The second phase of article screening will be done using a priori inclusion and exclusion criteria, titles and abstracts of papers will then be independently screened by two reviewers (JA and FA), to ensure no bias occurs.32 Ineligible papers will be excluded. Titles and abstracts that appear to meet the review’s eligibility criteria will be subjected to full-text reading. Any disagreement between the two reviewers will be resolved first through consensus. A tiebreaker (third reviewer (PO-O)) will adjudicate further disagreements on study eligibility. A PRISMA flow diagram will be used to demonstrate the review’s selection process and exclusion reasons, demonstrating replicability and transparency.38 This stage will represent an iterative process, incorporating search of the literature, refinement of search strategies and selection of articles.32

Stage 4: charting the data
The process of data extraction in scoping reviews is termed ‘charting’ the results.39 The charting process aims to generate a descriptive summary of the results that corresponds to the aims and research questions of the scoping review. A draft predetermined data charting form developed at the protocol stage will be used to retrieve data from included papers (see online supplemental additional file 3). Extracted data will include...
standard information (such as author, title, citation, country, year of publication), methodological data (such as study design, sample size, study aim/objectives, type of healthcare setting), patient characteristics (such as age, sex of study participants) and outcomes (such as prevalence, incidence of BWF, mortality, acute renal failure). To assure that all relevant data are collected adequately, the forms used for data extraction will be reviewed and piloted with at least five included articles by the research team prior to implementation. Data extraction will be conducted independently by two reviewers (CN and FO) before comparing forms. Differences will be discussed (if necessary with a third reviewer (GP)) before producing a single form containing the required data. The data charting form will include a category for reviewers to record emergent themes incase additional categories emerge during the data extraction process.

Stage 5: collating, summarising and reporting the results

The distinctive purpose of a scoping review is to agglomerate the findings and present an overview rather than a meta synthesis reporting results on narrowly defined questions done in systematic reviews.31 The main challenges to undertaking a scoping review focuses on determining a framework for presenting a narrative account.20 Considering this, the strategy of reporting results from this scoping review will base on recent innovations in reporting scoping review results, such as from Halas et al31 and Nelson et al.40 Both of the aforesaid studies advocate using a modified version of the PRISMA30 to present results from the search process. We will also modify the PRISMA checklist, specifically by integrating the elements of the checklist that are harmonious with the underpinnings of scoping review methodology while eliminating points that are not. Drawing further on the work of Levac et al29 and Nelson et al,40 we will also present a numerical overview of the amount, type and distribution of the included studies. The main section of the scoping review will comprise a thematic summary of the findings that relates the predetermined and emergent categories extracted from the included studies. The authors will discuss implications of the findings on future research, practice and policy.

Patient and public involvement

No patients involved.

Ethics and dissemination

The chosen methodology is based on the use of publicly available information and does not require ethical approval. The scoping review results will be disseminated in three ways: (1) submission of a policy report (2) publication in peer-reviewed journals and (3) presentation at national/international conferences.

Acknowledgements

We acknowledge Mbane Clinical Research Institute and Busitema University Faculty of Health sciences Library for the support offered.

Contributors

All authors have made substantive intellectual contributions to the development of this protocol. PO-0 and GP conceptualised the review approach and provided general guidance to the research team. All authors were involved in developing the review questions and the review design. GA has done the preliminary database search in PubMed. PO-0 identified the framework from which CN and FO developed and tested search terms. GP, JA and FA initially developed the data extraction framework which was then further developed by input from team members (FO and CN). GP initiated the first draft of the manuscript which was then followed by numerous iterations with substantial input and appraisal from all of the authors. PO-0 is the guarantor of the review. All authors approved the final version of the manuscript.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Supplemental material

This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

George Paasi http://orcid.org/0000-0001-6360-0589

REFERENCES

15 Olupot-Olupot P. The burden and spectrum of paediatric severe malaria and aetiology of dark urine syndrome in eastern Uganda. The Open University 2015.


