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Resurgence of Blackwater Fever among children in sub-Saharan Africa: A scoping Review protocol.

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Resurgence of Blackwater Fever among children in sub-Saharan Africa: A scoping Review protocol.

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ABSTRACT

Introduction:

Blackwater fever (BWF), a complication of malaria has in the past been considered 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 1960 to 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. Five electronic databases (MEDLINE via PubMed, Embase, the Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PsycInfo) will be systematically

searched using predefined keywords. In addition, reference lists of included articles and grey literature sources 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.

Keywords: Blackwater fever (BWF), resurgence, children, sub Saharan Africa (SSA), scoping review.

Article summary

Strength and limitations of the study

- A strength of this study is that a methodical and comprehensive search strategy as well as utilizing a broader analytical scope will enable full exploration of blackwater fever in children in SSA in terms of extent, range and nature of research done.
- A strength of this study is that it will utilise a broad review of multidisciplinary databases indexing high quality publications in the field of medicine, health and

education and the environment, these will provide a comprehensive assessment of published literature on childhood blackwater fever in SSA.

- A limitation of this study is that no formal quality assessment of included studies will be performed.
- A limitation of this study is that only peer-reviewed literature in English will be included, which will limit the scope of this review to articles published in English speaking countries or to those who published in English.

1. INTRODUCTION

Blackwater fever (BWF) is a clinical syndrome characterized by an acute intravascular haemolysis resulting in passing tea-coloured or coca cola urine [1, 2]. It is almost exclusive to *P. falciparum* malaria [3]. The first description of Blackwater fever (BWF) was from Africa by Easmon 1885, 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 (>3months) 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 attacks [3, 7] and recurrent synthetic aryl amino alcohol antimalarials exposure [8] such as quinine, mefloquine and halofantrine [9-12]. Some studies on the relationship between G6PD deficiency as a trigger of BWF are ambivalent. For insistence, while glucose-6-

phosphate dehydrogenase deficiency (G6PD) 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 G6PD deficiency[14]. Furthermore, the relationship between BWF and glucose-6-phosphate dehydrogenase deficiency (G6PDd) has been reported to be geographically-specific owing to the more severe phenotypes of G6PD deficiency variants in Mediterranean and Asian populations, compared to the milder African variant, which retains ~10-15% activity and thus less susceptible to oxidant-stress [15]. BWF has been conventionally used to describe *P. falciparum malaria* complicated by haemoglobinuria, however, recent studies by O'Donnell *et al* [2] and Olupot-Olupot [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 hyperlactatemia; suggesting hypoxic muscle cell injury from sequestration of parasitized red blood cells [2]. This suggests a multi-aetiological and pathophysiology process and hence the condition according to the two researchers is a syndrome called dark urine syndrome (DUS).

BWF has in the past been regarded as a rare complication of malaria in children living in high transmission settings [16-18]. More recently, however, a growing number of paediatric case-series have been published from both Africa [19-23] and Oceania [24]. Some studies have described the syndrome of BWF in which they documented varying prevalence of 6-48% [25, 26] and 11-59% [27, 28] 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 [29-31]. While it is evident a number of studies have been conducted on BWF in children in 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 January 1960 to November 2021. This novel study will establish the direction for the researchers on BWF in children and discuss the future agenda.

2. METHODS/DESIGN

According to Arksey and O'Malley [32], 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 [32].

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 [33]. The main strength of the scoping review method as applied to our study is that it allows for analysis of a broader research question however, a key limitation of this scoping review is that the quality of literature will not be assessed [34]. This scoping review aims to collate published literature on BWF in children in SSA. We will aim to map the breadth of literature on blackwater fever in children in sub Saharan Africa by categorizing articles to provide a thematic analysis of their content.

Scoping review protocol registration

This scoping review protocol has been registered with the Open Science Framework. Available: <https://doi.org/10.17605/OSF.IO/QNPKV>.

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 (POO, 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'Malley [32] with the methodological refinements proposed by Levac et al [35]. This process includes the following five steps illustrated in [figure 1](#) below:

We will also follow the PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation [36] (see [additional file 1](#)). The population–concept–context (PCC) framework [37] will also be used in this study to determine the eligibility criteria for potential articles to address the research question.

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 [32, 35]. 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 blackwater fever in children in SSA?
4. What is the paediatric case description of blackwater fever in SSA?
5. What are the leading thematic areas in childhood blackwater fever in SSA, what are their composition and relationships amongst them?
6. What are the emerging topics in childhood blackwater fever 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 (Population-Concept-Context) framework as recommended by the Joanna Briggs Institute for scoping reviews [38].

Eligibility criteria

The eligibility criteria were categorized according to the PCC framework.

Inclusion criteria:

Population

- Children

Concept

- Research articles reporting on blackwater fever in children in SSA carried out between 1960 and 2021 (1960 corresponds to the time when BWF become rare owing to quinine (which was a proven trigger of BWF) being increasingly replaced by chloroquine [39]. 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 sub Saharan Africa, a high malaria transmission region [40].
- 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 blackwater fever 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[38]. An experienced university librarian (GA) will conduct article search. Medical Subject headings (MeSH) 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 [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. Grey literature searches such as Websites of health and medical related organizations (World Health Organization (WHO), uptodate and Medscape will also be undertaken to identify any non-indexed literature of relevance to this review. 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 de-duplicates 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 blackwater fever in adults and studies on blackwater fever 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 [35]. 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 (POO)) 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 [41]. This stage will represent an iterative process, incorporating search of the literature, refinement of search strategies and selection of articles [35].

Stage 4: Charting the data

The process of data extraction in scoping reviews is termed ‘charting’ the results[42]. 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 [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 blackwater fever, 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 5 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 [34]. The main challenges to undertaking a scoping review focuses on determining a framework for presenting a narrative account [32]. 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 al [34] and Nelson et al [43]. Both of the aforesaid studies advocate using a modified version of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [41] 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, such as those points that relate to quality assessment/bias. Drawing further on the work of Levac et al [35] and Nelson et al [43], 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.

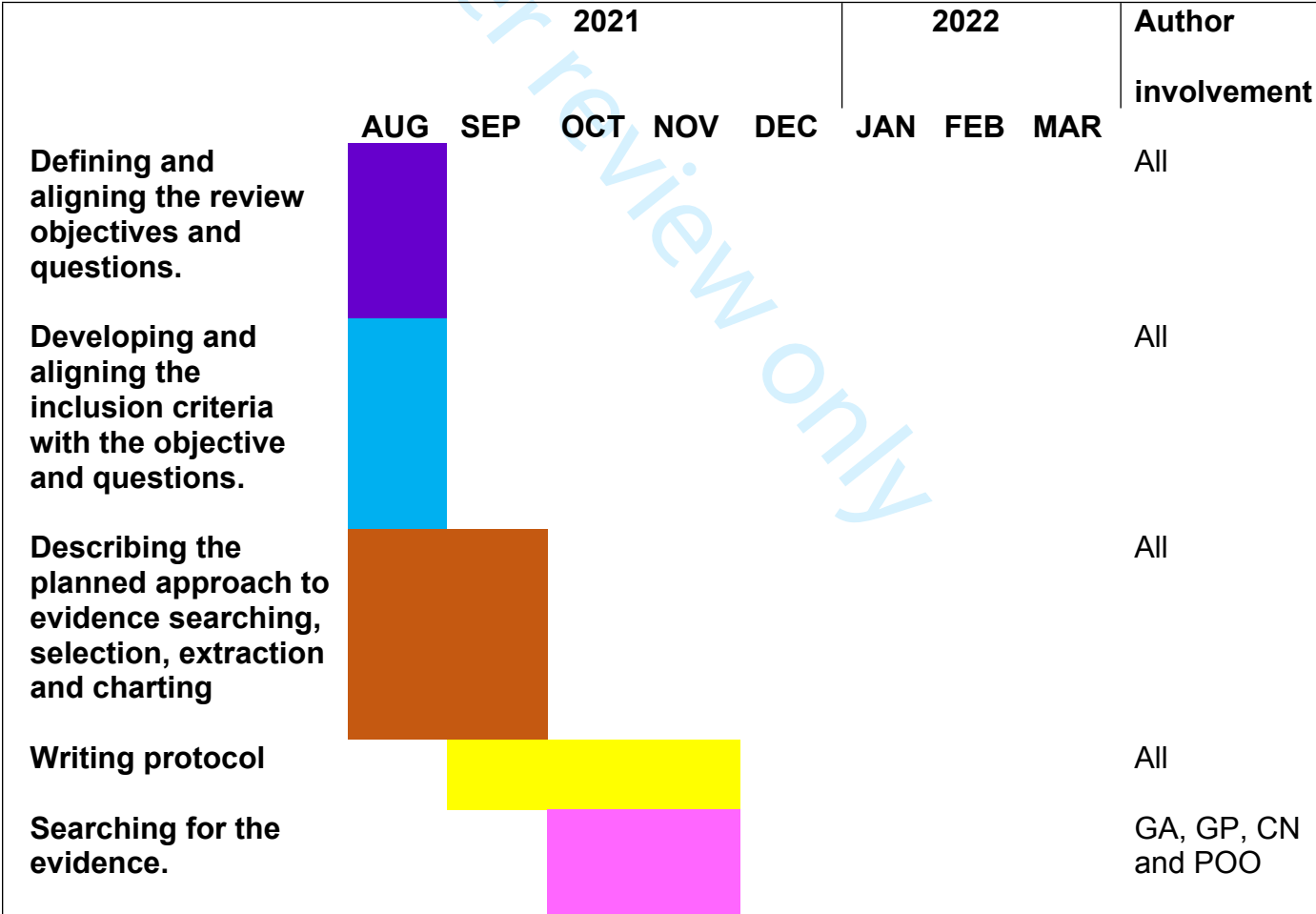
3. CONCLUSION

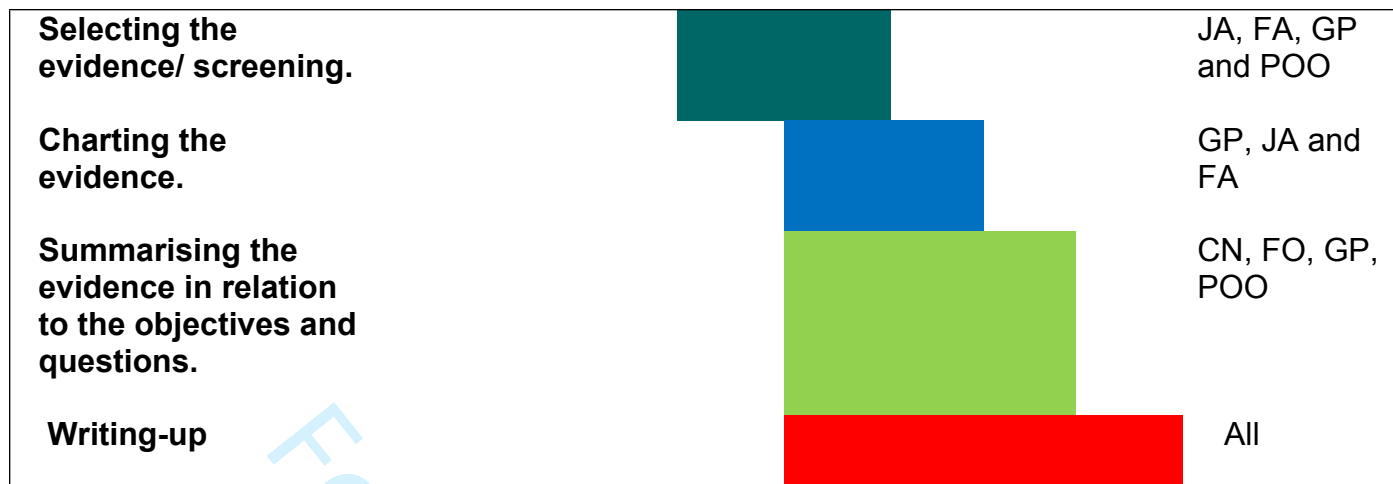
This protocol for methodically conducting a scoping review of published peer reviewed articles on blackwater fever in children in SSA from 1960 to 2021 has been presented.

This a priori protocol will guide the process of preparing for the scoping review in order to provide an approach that offers clarity, strength and transparency to avoid the inherent complex challenges that occur when undertaking a scoping review.

Results from this review will provide distinct insights into the resurgence of blackwater fever in children in SSA. This scoping review will have relevance to a variety of audiences including researchers, clinicians and policymakers interested in in-depth comprehension of the resurgence of blackwater fever in children in this region, blackwater fever mortality and morbidity impact on children and how to build the evidence base for this work in future.

Table 1 timeline for protocol and scoping review





Supplementary files

- 1.
- 2.
- 3.

List of abbreviations

BWF- Blackwater fever

PCC – Population, Concept, Context framework.

PRISMA-P - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Protocols.

MeSH – Medical Subject Headings

SSA – Sub Saharan Africa

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Author Contributions

All authors have made substantive intellectual contributions to the development of this protocol. POO 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. POO 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. POO is the guarantor of the review. All authors approve the final version of the manuscript.

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Availability of data & materials

The study data are available by request to the corresponding author.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval and consent to participate

The manuscript outlines a protocol for a scoping review that will undertake a secondary analysis of data already collected (from human participants) and does not require ethical approval.

Provenance and peer review

Not commissioned; externally peer reviewed.

Consent to Publish

The Mbale Clinical Research Institute (MCRI, www.mcri.ac.ug), a research entity affiliated to the Uganda National Health Research Organization, approved the publication of this manuscript.

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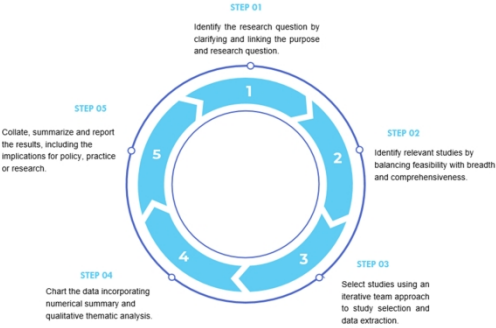
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Figure 1.

Figure 1

Figure 1 Scoping review methodological steps outlined by Arksey and O'Malley.



338x190mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title:		Resurgence of Blackwater Fever among children in sub Saharan Africa: A scoping Review protocol.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2, 39, 122
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	<input checked="" type="checkbox"/>	<input type="checkbox"/>	133-134
Authors:					
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4-16, 328-331
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	317-327
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Support:					
Sources	5a	Indicate sources of financial or other support for the review	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	65-114
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	160-170
METHODS					

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	<input type="checkbox"/>	178-201
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	<input type="checkbox"/>	202-205
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input type="checkbox"/>	Additional File 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>	227-228
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	<input type="checkbox"/>	229-245
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input type="checkbox"/>	247-263
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	<input type="checkbox"/>	264-268
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input type="checkbox"/>	252-256
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	N/A
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	<input checked="" type="checkbox"/>	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	<input checked="" type="checkbox"/>	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	278-280
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	<input checked="" type="checkbox"/>	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Search strategies: _PUBMED. Search strategy

Resurgence of Blackwater Fever among children in sub Saharan Africa: A scoping Review protocol.

Preliminary search: done on 15 November 2021

("Blackwater fever" OR "Blackwater Fevers" OR "Fever, Blackwater" OR "Fevers, Blackwater" OR "Malaria, Hemolytic" OR "Hemolytic Malaria" OR "Hemolytic Malarias" OR "Malarias, Hemolytic" OR "Black Water Fever" OR "Black Water Fevers" OR "Fever, Black Water" OR "Fevers, Black Water" OR "haemoglobinuria" OR "dark urine syndrome")

AND

(Children)

AND

(Sub Saharan Africa OR SSA OR Africa OR africa south of the sahara OR africa, central OR africa, southern OR africa, eastern OR africa, western OR Angola OR benin OR botswana OR burkina faso OR burundi OR cabo verde OR Cape Verde OR cameroon OR central african republic OR chad OR democratic republic of the congo OR congo Brazzaville OR Côte d'Ivoire OR Ivory Coast OR equatorial guinea OR eritrea OR ethiopia OR gabon OR gambia OR ghana OR guinea OR guinea bissau OR kenya OR lesotho OR liberia OR Madagascar OR malawi OR mali OR mauritania OR Mauritius OR morocco OR mozambique OR namibia OR niger OR nigeria OR rwanda OR Sao Tome and Principe OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR south sudan OR sudan OR Swaziland OR tanzania OR togo OR tunisia OR uganda OR zambia OR Zimbabwe)

Hits: 89

Resurgence of blackwater fever in children in SSA: A scoping review Data charting form

S/N	Study ID (title, year of publication, citation)	Author, study site and period
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For peer review only

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Malaria endemicity, study design and sample size Study aims and findings

For peer review only

Aetiology of BWF and outcomes comments/ emerging themes

For peer review only

BMJ Open

Resurgence of Blackwater Fever among children in sub-Saharan Africa: A scoping Review protocol.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059875.R1
Article Type:	Protocol
Date Submitted by the Author:	03-May-2022
Complete List of Authors:	Paasi, George; Busitema University; Mbale Clinical Research institute Ndila, Carolyne; Mbale Clinical Research Institute (MCRI) Alaroker, Florence; Soroti Regional Referral Hospital, Department of Paediatric and Child Health Abeso, Julian; Mbale Regional Referral Hospital, Department of Paediatric and Child Health Asiimwe, Glorias; Busitema University, Faculty of Health Sciences university library Okello, Francis; Busitema University, Department of Public Health Olupot-Olupot, Peter; Mbale Clinical Research Institute (MCRI); Busitema University, Department of Public Health
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Paediatrics
Keywords:	EPIDEMIOLOGY, INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts

Resurgence of Blackwater Fever among children in sub-Saharan Africa: A scoping Review protocol.

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ABSTRACT

Introduction:

Blackwater fever, a complication of malaria has in the past been considered a rare complication of malaria in children living in high transmission settings. More recently, however, a growing number of paediatric clusters of blackwater fever cases have been reported predominantly in sub Saharan Africa (SSA). The aim of this study is to map evidence on blackwater fever among children in SSA from 01/01/1960 to 31/12/2021.

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 psycinfo) 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 blackwater fever in SSA and identify its research gaps in SSA. We will be disseminating results through journals and conferences targeting primary care providers.

Keywords: Blackwater fever, resurgence, children, sub Saharan Africa (SSA), scoping review.

Article summary

Strength and limitations of the study

- A strength of this study is that a methodical and comprehensive search strategy as well as utilizing a broader analytical scope will enable full exploration of blackwater fever in children in SSA in terms of extent, range and nature of research done.

- A strength of this study is that it will utilise a broad review of multidisciplinary databases indexing high quality publications in the field of medicine, health and education and the environment, these will provide a comprehensive assessment of published literature on childhood blackwater fever in SSA.
- A strength of this study is that a formal quality assessment of included studies will be performed using the guidance from the Joanna Briggs Institute website.
- A limitation of this study is that only peer-reviewed literature in English will be included, which will limit the scope of this review to articles published in English speaking countries or to those who published in English.

1. INTRODUCTION

Blackwater fever is a clinical syndrome characterized by an acute intravascular haemolysis resulting in passing tea-coloured or coca cola urine [1, 2]. It is almost exclusive to *P. Falciparum* malaria [3]. The first description of Blackwater fever was from Africa by Easmon 1885, 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 (>3months) 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 blackwater fever resulted from interaction between host response to repeated *P. Falciparum* malarial attacks [3, 7] and recurrent synthetic aryl amino alcohol antimalarials

exposure [8] such as quinine, mefloquine and halofantrine [9-12]. Some studies on the relationship between Glucose-6 Phosphate Dehydrogenase deficiency as a trigger of blackwater fever are ambivalent. For instance, while glucose-6-phosphate dehydrogenase deficiency 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 Glucose-6 Phosphate Dehydrogenase deficiency[14]. Furthermore, the relationship between blackwater fever and glucose-6-phosphate dehydrogenase deficiency has been reported to be geographically-specific owing to the more severe phenotypes of Glucose-6 Phosphate Dehydrogenase deficiency variants in Mediterranean and Asian populations, compared to the milder African variant, which retains ~10-15% activity and thus less susceptible to oxidant-stress [15]. blackwater fever has been conventionally used to describe *P. Falciparum malaria* complicated by haemoglobinuria, however, recent studies by O'Donnell *et al* [2] and Olupot-Olupot [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 hyperlactatemia; suggesting hypoxic muscle cell injury from sequestration of parasitized red blood cells [2]. This suggests a multi-aetiological and pathophysiology process and hence the condition according to the two researchers is a syndrome called dark urine syndrome (DUS).

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Blackwater fever has in the past been regarded as a rare complication of malaria in children living in high transmission settings [16-18]. More recently, however, a growing number of paediatric case-series have been published from both Africa [19-23] and Oceania [24]. Some studies have described the syndrome of blackwater fever in which they documented varying prevalence of 6-48% [25, 26] and 11-59% [27, 28] of patients with severe malaria respectively. Evidence from the past three decades underscores the resurgence of blackwater fever in children though these descriptions remain incomplete. Potential reasons for these trends are varied, but geographical localisation of blackwater fever together with fewer research resources directed towards its epidemiology, pathophysiology and interventions may play a role [29-31]. While it is evident a number of studies have been conducted on blackwater fever in children in 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 blackwater fever 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 blackwater fever in SSA. The main objective of this study is to map evidence on blackwater fever in children in SSA from 01/01/1960 to 31/12/2021. This novel study will establish the direction for the researchers on blackwater fever in children and discuss the future agenda.

2. METHODS/DESIGN

According to Arksey and O'Malley [32], 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 [32].

We will undertake a scoping review of published scientific literature on blackwater fever in children in SSA as the preferred method of evidence synthesis to explore and map the resurgence of blackwater fever in this population. This methodology is particularly important in comprehensively and systematically mapping the literature and identifying key concepts, theories, evidence, or research gaps [33]. The main strength of the scoping review method as applied to our study is that it allows for analysis of a broader research question [34]. This scoping review aims to collate published literature on blackwater fever in children in SSA. We will aim to map the breadth of literature on blackwater fever in children in sub Saharan Africa by categorizing articles to provide a thematic analysis of their content.

Scoping review protocol registration

This scoping review protocol has been registered with the Open Science Framework. Available: <https://doi.org/10.17605/OSF.IO/QNPKV>.

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 (POO, 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.

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3 **Protocol design**

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5 This review will follow the methodological steps outlined by Arksey and O'Malley [32] with

6 the methodological refinements proposed by Levac et al [35]. This process includes the

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8 following five steps illustrated in [figure 1](#) below:

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11 We will also follow the PRISMA extension for scoping reviews (PRISMA-scr): checklist

12 and explanation [36] (see [additional file 1](#)). The population–concept–context (PCC)

13 framework [37] will also be used in this study to determine the eligibility criteria for

14 potential articles to address the research question. This scoping review will be

15 conducted until 31/October/2022.

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26 **Stage 1: Identifying the research questions**

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28 According to Arksey and O'Malley, the first stage in the process of conducting a scoping

29 review is to identify the research question(s) for the study and to link the question with

30 purpose of the study [32, 35]. Bearing that in mind, the team developed a series of

31 research questions related to the aims of the study through an iterative process. Since in

32 addition to iteration, the process of conducting a scoping review requires a reflexive

33 approach to each stage as the team becomes increasingly familiar with the literature,

34 there is a possibility that revisions may be made to the research questions. Six research

35 questions were identified to guide the scoping review.

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

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- 49 1. What are the volume, year wise distribution and journal wise distribution of peer-
- 50 reviewed published literature on blackwater fever in children in SSA?
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2. What are the trends in publications and citation of peer-reviewed published literature on blackwater fever in children in SSA?
3. What is the aggregate prevalence of blackwater fever in children in SSA?
4. What is the paediatric case description of blackwater fever in SSA?
5. What are the leading thematic areas in childhood blackwater fever in SSA, what are their composition and relationships amongst them?
6. What are the emerging topics in childhood blackwater fever 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 (Population-Concept-Context) framework as recommended by the Joanna Briggs Institute for scoping reviews [38].

Eligibility criteria

The eligibility criteria were categorized according to the PCC framework.

Inclusion criteria:

Population

- Children

Concept

- Research articles reporting on blackwater fever in children in SSA carried out between 01/01/1960 and 31/12/2021 (01/01/1960 corresponds to the time when

blackwater fever become rare owing to quinine (which was a proven trigger of blackwater fever) being increasingly replaced by chloroquine [39]. However, in the past three decades, there has been an increasing number of blackwater fever reports published especially in SSA). The selected time range will enable exploration of the resurgence of blackwater fever in this region.

Context

- Research articles are limited to sub Saharan Africa, a high malaria transmission region [40].
- 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 blackwater fever 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[38]. An experienced university librarian (GA) will conduct article search. Medical Subject headings (mesh) 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 [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 de-duplicates 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 blackwater fever in adults and studies on blackwater fever 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 [35]. 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 (POO)) 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 [41]. This stage will represent an iterative process, incorporating search of the literature, refinement of search strategies and selection of articles [35].

Stage 4: Charting the data

The process of data extraction in scoping reviews is termed ‘charting’ the results[42]. 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 [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 blackwater fever, 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 5 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.

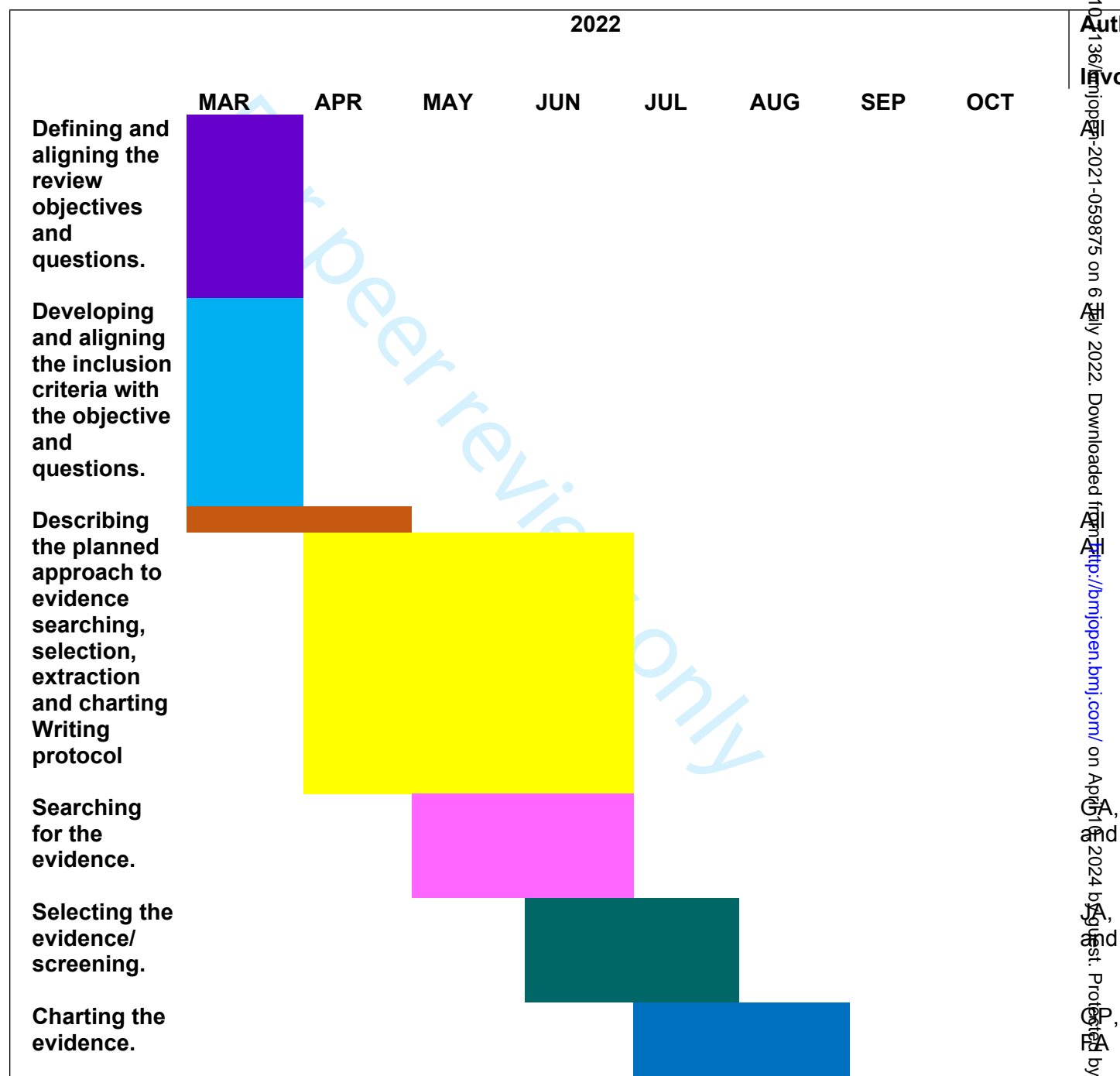
Stage 5: Collating, summarising and reporting the results

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 [34]. The main challenges to undertaking a scoping review focuses on determining a framework for presenting a narrative account [32]. 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 al [34] and Nelson et al [43]. Both of the aforesaid studies advocate using a modified version of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [41] 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 al [35] and Nelson et al [43], 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.

For peer review only

Table 1 timeline for protocol and scoping review

Summarising the evidence in relation to the objectives and questions.	
Writing-up	

Supplementary files

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List of abbreviations

PCC – Population, Concept, Context framework.

PRISMA-P - Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.

Mesh – Medical Subject Headings

SSA – Sub Saharan Africa

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Author Contributions

All authors have made substantive intellectual contributions to the development of this protocol. POO 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. POO 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. POO is the guarantor of the review. All authors approve the final version of the manuscript.

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Availability of data & materials

The study data are available by request to the corresponding author.

Conflict of interest

The authors declare no conflict of interest.

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3 **Ethics approval and consent to participate**

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5 The manuscript outlines a protocol for a scoping review that will undertake a secondary

6 analysis of data already collected (from human participants) and does not require

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8 ethical approval.

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13 **Provenance and peer review**

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15 Not commissioned; externally peer reviewed.

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19 **Consent to Publish**

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21 The Mbale Clinical Research Institute (MCRI, www.mcric.ac.ug), a research entity

22 affiliated to the Uganda National Health Research Organization, approved the

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24 publication of this manuscript.

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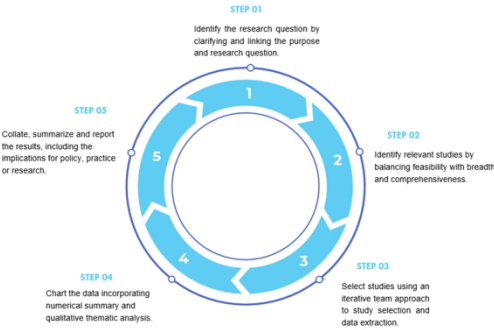
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Figure 1.

Figure 1

Figure 1 Scoping review methodological steps outlined by Arksey and O'Malley.



338x190mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION			on 6 July 2024		
Title:		Resurgence of Blackwater Fever among children in sub Saharan Africa: A scoping Review protocol.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2, 41, 126
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	<input checked="" type="checkbox"/>	<input type="checkbox"/>	137-138
Authors:			https://doi.org/10.1111/j.1365-2703.2024.01111.x		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4-16, 358-360
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	347-356
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Support:			on April 10, 2024 by guest.		
Sources	5a	Indicate sources of financial or other support for the review	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	68-118
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	172-182
METHODS					

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	<input type="checkbox"/>	187-213
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	<input type="checkbox"/>	214-217
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input type="checkbox"/>	Additional File 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>	260-275
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	<input type="checkbox"/>	242-257
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input type="checkbox"/>	260-275
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	<input type="checkbox"/>	264-268
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input type="checkbox"/>	267-268
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input type="checkbox"/>	60-61
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	<input checked="" type="checkbox"/>	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	<input checked="" type="checkbox"/>	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	290-292
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	<input checked="" type="checkbox"/>	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

For peer review only

Search strategies: _PUBMED. Search strategy

Resurgence of Blackwater Fever among children in sub Saharan Africa: A scoping Review protocol.

Preliminary search: done on 15 November 2021

("Blackwater fever" OR "Blackwater Fevers" OR "Fever, Blackwater" OR "Fevers, Blackwater" OR "Malaria, Hemolytic" OR "Hemolytic Malaria" OR "Hemolytic Malaras" OR "Malaras, Hemolytic" OR "Black Water Fever" OR "Black Water Fevers" OR "Fever, Black Water" OR "Fevers, Black Water" OR "haemoglobinuria" OR "dark urine syndrome" OR "tea-coloured urine" OR "coca-cola coloured urine")

AND

(Children)

AND

(Sub Saharan Africa OR SSA OR Africa OR africa south of the sahara OR africa, central OR africa, southern OR africa, eastern OR africa, western OR Angola OR benin OR botswana OR burkina faso OR burundi OR cabo verde OR Cape Verde OR cameroon OR central african republic OR chad OR democratic republic of the congo OR congo Brazzaville OR Côte d'Ivoire OR Ivory Coast OR equatorial guinea OR eritrea OR ethiopia OR gabon OR gambia OR ghana OR guinea OR guinea bissau OR kenya OR lesotho OR liberia OR Madagascar OR malawi OR mali OR mauritania OR Mauritius OR morocco OR mozambique OR namibia OR niger OR nigeria OR rwanda OR Sao Tome and Principe OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR south sudan OR sudan OR Swaziland OR tanzania OR togo OR tunisia OR uganda OR zambia OR Zimbabwe)

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Resurgence of blackwater fever in children in SSA: A scoping review Data charting form
S/N Study ID (title, year of publication, citation Author, study site and period

For peer review only

Malaria endemicity, study design and sample size Study aims and findings

For peer review only

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Aetiology of BWF and outcomes comments/ emerging themes

For peer review only

BMJ Open

Resurgence of Blackwater Fever among children in sub-Saharan Africa: A scoping Review protocol.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059875.R2
Article Type:	Protocol
Date Submitted by the Author:	11-Jun-2022
Complete List of Authors:	Paasi, George; Busitema University; Mbale Clinical Research institute Ndila, Carolyne; Mbale Clinical Research Institute (MCRI) Alaroker, Florence; Soroti Regional Referral Hospital, Department of Paediatric and Child Health Abeso, Julian; Mbale Regional Referral Hospital, Department of Paediatric and Child Health Asiimwe, Glorias; Busitema University, Faculty of Health Sciences university library Okello, Francis; Busitema University, Department of Public Health Olupot-Olupot, Peter; Mbale Clinical Research Institute (MCRI); Busitema University, Department of Public Health
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Paediatrics
Keywords:	EPIDEMIOLOGY, INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, Tropical medicine < INFECTIOUS DISEASES

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Manuscripts

Resurgence of Blackwater Fever among children in sub-Saharan Africa: A scoping Review protocol.

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ABSTRACT

Introduction:

Blackwater fever (BWF), a complication of malaria has in the past been considered 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 01/01/1960 to 31/12/2021.

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 PsycInfo) 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.

Keywords: Blackwater fever, resurgence, children, sub Saharan Africa, scoping review.

Article summary

Strength and limitations of the study

- A strength of this study is that a methodical and comprehensive search strategy as well as utilizing a broader analytical scope will enable full exploration of BWF in children in SSA in terms of extent, range and nature of research done.
- A strength of this study is that it will utilise a broad review of multidisciplinary databases indexing high quality publications in the field of medicine, health and

education and the environment, these will provide a comprehensive assessment of published literature on childhood BWF in SSA.

- A strength of this study is that a formal quality assessment of included studies will be performed using the guidance from the Joanna Briggs Institute website.
- A limitation of this study is that only peer-reviewed literature in English will be included, which will limit the scope of this review to articles published in English speaking countries or to those who published in English.

1. INTRODUCTION

BWF is a clinical syndrome characterized by an acute intravascular haemolysis resulting in passing tea-coloured or coca cola urine [1, 2]. It is almost exclusive to *P. Falciparum* malaria [3]. The first description of BWF was from Africa by Easmon 1885, 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 (>3months) 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 attacks [3, 7] and recurrent synthetic aryl amino alcohol antimalarials exposure [8] 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 [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 to the milder African variant, which retains ~10-15% activity and thus less susceptible to oxidant-stress [15]. BWF has been conventionally used to describe *P. Falciparum malaria* complicated by haemoglobinuria, however, recent studies by O'Donnell *et al* [2] and Olupot-Olupot [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 hyperlactatemia; suggesting hypoxic muscle cell injury from sequestration of parasitized red blood cells [2]. This suggests a multi-aetiological and pathophysiology process and hence the condition according to the two researchers is a syndrome called dark urine syndrome (DUS).

BWF has in the past been regarded as a rare complication of malaria in children living in high transmission settings [16-18]. More recently, however, a growing number of paediatric case-series have been published from both Africa [19-23] and Oceania [24]. Some studies have described the syndrome of BWF in which they documented varying prevalence of 6-48% [25, 26] and 11-59% [27, 28] 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 [29-31]. While it is evident a number of studies have been conducted on BWF in children in 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 01/01/1960 to 31/12/2021. This novel study will establish the direction for the researchers on BWF in children and discuss the future agenda.

2. METHODS/DESIGN

According to Arksey and O'Malley [32], 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 [32].

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 [33]. The main strength of the scoping review method as applied to our study is that it allows for analysis of a broader research question [34]. 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 categorizing articles to provide a thematic analysis of their content.

Scoping review protocol registration

This scoping review protocol has been registered with the Open Science Framework. Available: <https://doi.org/10.17605/OSF.IO/QNPKV>.

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 (POO, 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'Malley [32] with the methodological refinements proposed by Levac et al [35]. This process includes the following five steps illustrated in [figure 1](#) below:

We will also follow the PRISMA extension for scoping reviews (PRISMA-scr): checklist and explanation [36] (see [additional file 1](#)). The population–concept–context (PCC) framework [37] 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 01/03/2022 to 30/10/2022.

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 [32, 35]. 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 amongst 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 (Population-Concept-Context) framework as recommended by the Joanna Briggs Institute for scoping reviews [38].

Eligibility criteria

The eligibility criteria were categorized according to the PCC framework.

Inclusion criteria:

Population

- Children

Concept

- Research articles reporting on BWF in children in SSA carried out between 01/01/1960 and 31/12/2021 (01/01/1960 corresponds to the time when BWF become rare owing to quinine (which was a proven trigger of BWF) being increasing replaced by chloroquine [39]. 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 [40].
- 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[38]. An experienced university librarian (GA) will conduct article search. Medical Subject headings (mesh) 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 [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 de-duplicates 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 [35]. 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 (POO)) 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 [41]. This stage will represent an iterative process, incorporating search of the literature, refinement of search strategies and selection of articles [35].

Stage 4: Charting the data

The process of data extraction in scoping reviews is termed ‘charting’ the results[42]. 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 [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 5 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 [34]. The main challenges to undertaking a scoping review focuses on determining a framework for presenting a narrative account [32]. Considering

1
2
3 this, the strategy of reporting results from this scoping review will base on recent
4 innovations in reporting scoping review results, such as from Halas et al [34] and Nelson
5 et al [43]. Both of the aforesaid studies advocate using a modified version of the Preferred
6 Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [41] to present
7 results from the search process. We will also modify the PRISMA checklist, specifically
8 by integrating the elements of the checklist that are harmonious with the underpinnings
9 of scoping review methodology while eliminating points that are not. Drawing further on
10 the work of Levac et al [35] and Nelson et al [43], we will also present a numerical
11 overview of the amount, type and distribution of the included studies. The main section of
12 the scoping review will comprise a thematic summary of the findings that relates the
13 predetermined and emergent categories extracted from the included studies. The authors
14 will discuss implications of the findings on future research, practice and policy.

31 **Patient and public involvement**

32 No patients involved.

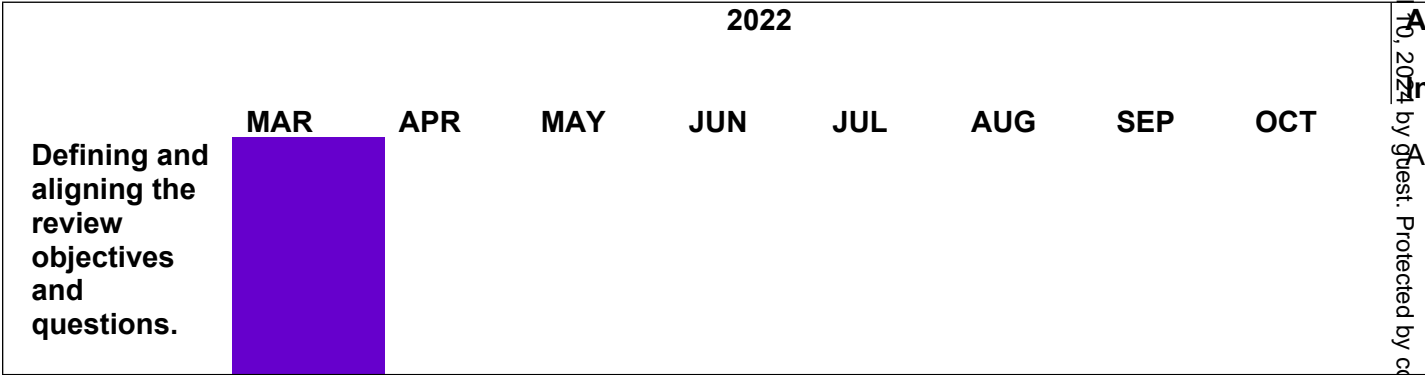
37 **Ethics and dissemination**

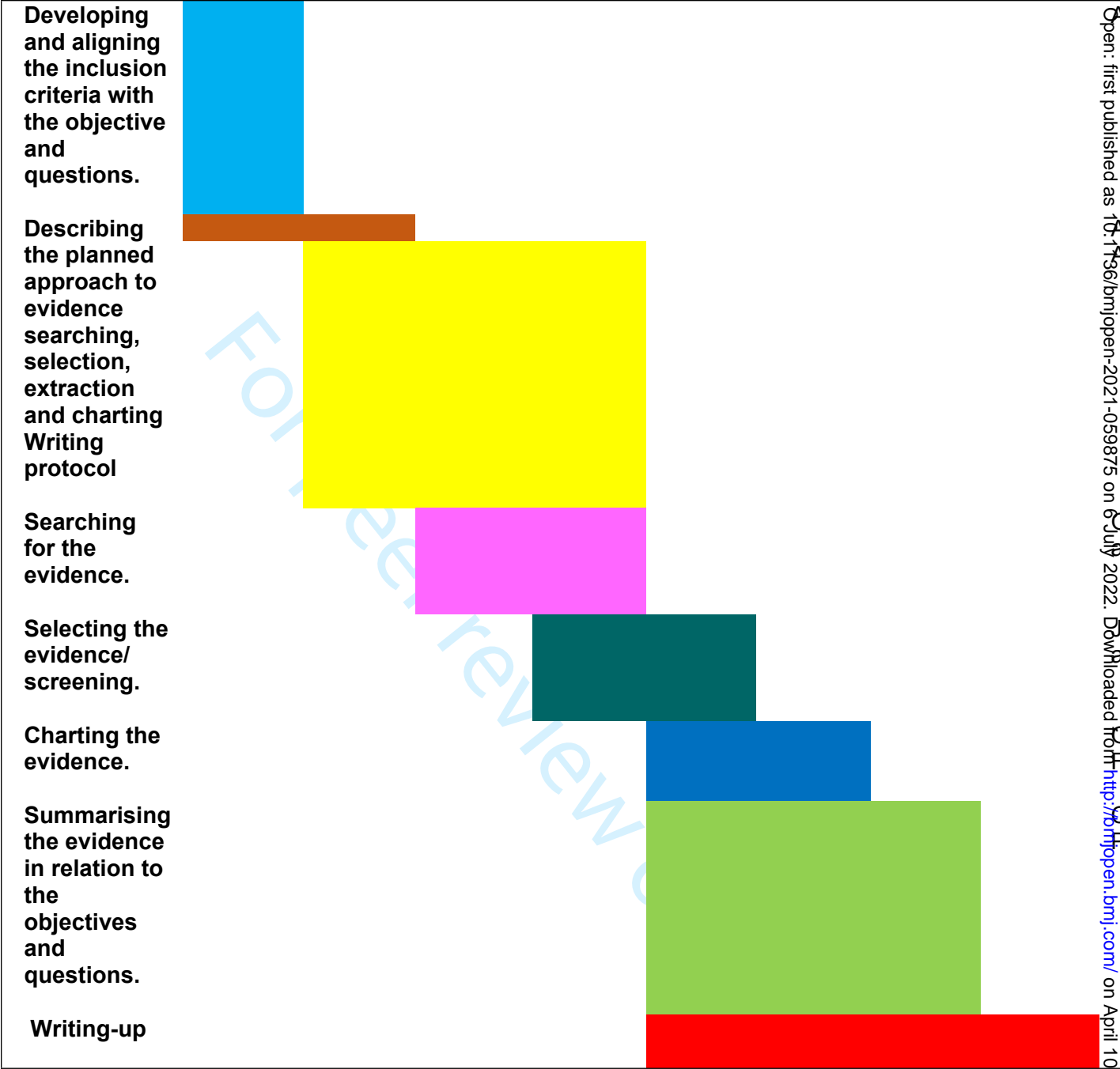
38 The chosen methodology is based on the use of publicly available information and does
39 not require ethical approval. The scoping review results will be disseminated in three
40 ways: (1) submission of a policy report (2) publication in peer-reviewed journals and (3)
41 presentation at national/international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





Supplementary files

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3 **List of abbreviations**

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- 5 BWF – Blackwater fever
- 6
- 7
- 8 G6PDd – Glucose-6 phosphate dehydrogenase deficiency
- 9
- 10 PCC – Population, Concept, Context framework.
- 11
- 12 PRISMA-P - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- 13
- 14 Protocols.
- 15
- 16
- 17 Mesh – Medical Subject Headings
- 18
- 19 SSA – Sub Saharan Africa
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23

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34 commercial or not-for-profit sectors.

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38 **Author Contributions**

39

40 All authors have made substantive intellectual contributions to the development of this

41

42 protocol. POO and GP conceptualised the review approach and provided general

43

44 guidance to the research team. All authors were involved in developing the review

45

46 questions and the review design. GA has done the preliminary database search in

47

48 pubmed. POO identified the framework from which CN and FO developed and tested

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50 search terms. GP, JA and FA initially developed the data extraction framework which

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52 was then further developed by input from team members (FO and CN). GP initiated the

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first draft of the manuscript which was then followed by numerous iterations with substantial input and appraisal from all of the authors. POO is the guarantor of the review. All authors approve the final version of the manuscript.

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Availability of data & materials

The study data are available by request to the corresponding author.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval and consent to participate

The manuscript outlines a protocol for a scoping review that will undertake a secondary analysis of data already collected (from human participants) and does not require ethical approval.

Provenance and peer review

Not commissioned; externally peer reviewed.

Consent to Publish

The Mbale Clinical Research Institute (MCRI, www.mcric.ac.ug), a research entity affiliated to the Uganda National Health Research Organization, approved the publication of this manuscript.

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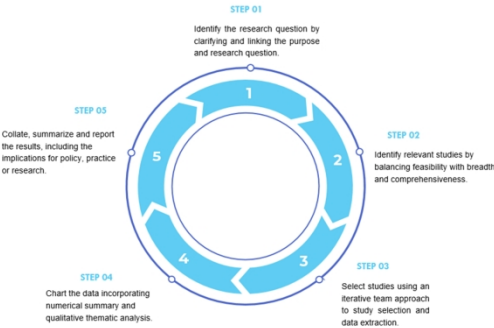
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Figure 1.

Figure 1

Figure 1 Scoping review methodological steps outlined by Arksey and O'Malley.

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338x190mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title:		Resurgence of Blackwater Fever among children in sub Saharan Africa: A scoping Review protocol.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	2, 41, 126
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	<input checked="" type="checkbox"/>	<input type="checkbox"/>	137-138
Authors:					
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	4-16, 358-360
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	347-356
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Support:					
Sources	5a	Indicate sources of financial or other support for the review	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	68-118
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	172-182
METHODS					

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	<input type="checkbox"/>	187-213
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	<input type="checkbox"/>	214-217
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input type="checkbox"/>	Additional File 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>	260-275
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	<input type="checkbox"/>	242-257
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input type="checkbox"/>	260-275
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	<input type="checkbox"/>	264-268
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input type="checkbox"/>	267-268
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input type="checkbox"/>	60-61
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	<input checked="" type="checkbox"/>	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	<input checked="" type="checkbox"/>	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	290-292
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	<input checked="" type="checkbox"/>	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Search strategies: _PUBMED. Search strategy

Resurgence of Blackwater Fever among children in sub Saharan Africa: A scoping Review protocol.

Preliminary search: done on 15 November 2021

("Blackwater fever" OR "Blackwater Fevers" OR "Fever, Blackwater" OR "Fevers, Blackwater" OR "Malaria, Hemolytic" OR "Hemolytic Malaria" OR "Hemolytic Malaras" OR "Malaras, Hemolytic" OR "Black Water Fever" OR "Black Water Fevers" OR "Fever, Black Water" OR "Fevers, Black Water" OR "haemoglobinuria" OR "dark urine syndrome" OR "tea-coloured urine" OR "coca-cola coloured urine")

AND

(Children)

AND

(Sub Saharan Africa OR SSA OR Africa OR africa south of the sahara OR africa, central OR africa, southern OR africa, eastern OR africa, western OR Angola OR benin OR botswana OR burkina faso OR burundi OR cabo verde OR Cape Verde OR cameroon OR central african republic OR chad OR democratic republic of the congo OR congo Brazzaville OR Côte d'Ivoire OR Ivory Coast OR equatorial guinea OR eritrea OR ethiopia OR gabon OR gambia OR ghana OR guinea OR guinea bissau OR kenya OR lesotho OR liberia OR Madagascar OR malawi OR mali OR mauritania OR Mauritius OR morocco OR mozambique OR namibia OR niger OR nigeria OR rwanda OR Sao Tome and Principe OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR south sudan OR sudan OR Swaziland OR tanzania OR togo OR tunisia OR uganda OR zambia OR Zimbabwe)

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Resurgence of blackwater fever in children in SSA: A scoping review Data charting form
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Malaria endemicity, study design and sample size Study aims and findings

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Aetiology of BWF and outcomes comments/ emerging themes

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