The resurgence of blackwater fever among children in sub-Saharan Africa: A scoping Review

Paasi George

georgepaasi8@gmail.com

Mbale clinical research institute (MCRI) https://orcid.org/0000-0001-6360-0589

Namazi Ruth

Makerere University, college of health sciences

Malaika Nancy

Makerere University, college of health sciences

Cate Namayanja

Mbale clinical research institute, Mbale Uganda

Paul Ongodia

Mbale clinical research institute, Mbale Uganda

Charles Benard Okalebo

Mbale clinical research institute, Mbale Uganda

Denis Amorut

Mbale clinical research institute, Mbale Uganda

Glorias Asiimwe

Busitema University Faculty of Health Sciences Library

Francis Okello

Busitema University Faculty of Health Sciences, department of public Health

David Mukunya

Busitema University Faculty of Health Sciences, department of public Health https://orcid.org/0000-0002-3892-9777

Ian Guyton Munabi

Makerere University, College of Health sciences, school of medicine.

Sarah Kiguli

Makerere University, College of Health sciences, school of medicine. https://orcid.org/0000-0002-8764-4161

Richard Idro

Makerere University, College of Health sciences, school of medicine.

Peter Olupot-Olupot

Mbale clinical research institute, Mbale Uganda https://orcid.org/0000-0002-5757-609X

Systematic Review

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Abstract

Background:

Blackwater fever (BWF), a life-threatening complication of *Plasmodium falciparum* malaria, has re-emerged as a significant health concern among children in sub-Saharan Africa (SSA). Characterized by acute intravascular hemolysis, hemoglobinuria, and severe anemia, BWF necessitates urgent medical intervention. Despite its clinical severity, data on its burden, risk factors, and management remain fragmented. Therefore, this scoping review aimed to systematically map the existing literature on BWF in SSA, focusing on its epidemiology, clinical presentation, risk factors, management strategies, and outcomes among children in SSA.

Methods:

Following the Arksey and O'Malley framework, a comprehensive search was conducted across six databases (PubMed, Embase, Cochrane Library, CINAHL, PsycINFO, web of science) and grey literature sourcesincluding preprint servers, conference proceedings, theses, dissertations, WHO reports and clinical trials registries (PACTR, clinicaltrials.gov). Studies published from inception to December 2024 were included. Data were extracted and synthesized narratively, with findings categorized thematically by epidemiology, clinical features, risk factors, management, and outcomes.

Results:

BWF was geographical clustered in East and Central Africa, particularly Uganda (53.8%) and the DRC (26.9%). Prevalence ranged from 4.4% to 52.7%, with higher incidence during rainy seasons. MBL2 AA polymorphisms, elevated IgG1 and quinine exposure (aOR 50.19-57.33) were significant contributors while G6PD deficiency (G6PDd) had conflicting associations. Clinical hallmarks were dark urine (100% of cases), jaundice (22.7-100%), and severe anemia (23.7-77%) aligning with the "hemolytic triad" reported in BWF. Acute kidney injury (AKI) (16.2-90.6% of cases) and recurrent episodes (50-68% readmission rates) exacerbated morbidity. Diagnosis relied on clinical criteria, with limited laboratory confirmation, while management emphasized artemisinin-based therapies and supportive care. Delays in blood transfusions and renal replacement therapy contributed to poor outcomes.

Conclusion:

BWF resurgence in SSA highlights critical gaps in diagnostics, equitable care, and adherence to artemisinin-based treatments. Targeted surveillance during malaria peaks, standardized diagnostic protocols, and improved access to supportive therapies are urgently needed to mitigate BWF-associated mortality and morbidity in high-burden regions.

Trial registration: OSF https://doi.org/10.17605/OSF.IO/QNPKV

Introduction

BWF, a life-threatening complication of *Plasmodium falciparum* malaria, represents a critical yet neglected health challenge for children in SSA. It is characterized by acute intravascular hemolysis, hemoglobinuria, and severe anemia often resulting into passing of dark urine or tea-coloured urine or coca-cola urine (1, 2). BWF necessitates urgent interventions such as blood transfusions and renal replacement therapy to avert prolonged hospitalisation (3), recurrent hospitalizations (4, 5) and AKI (6). However, in resource-limited malaria-endemic regions, these interventions are often inaccessible, leading to fatality rates exceeding 20% among hospitalized children (7). Compounding this burden, over 50% of survivors experience recurrent episodes, driving repeated hospitalizations and perpetuating cycles of morbidity (8).

Historically, BWF was considered rare complication of malaria (9–11), primarily affecting non-immune European adults in the early 20th century during quinine-based malaria treatment (12–14). Its incidence declined mid-century with chloroquine adoption (15–17) but re-emerged in the 2000s alongside the widespread rollout of artemisinin-based combination therapies (ACTs) (18–20). Once considered rare in African pediatric populations, BWF now contributes significantly to severe malaria morbidity and mortality, reflecting shifts in epidemiology and risk factors (17, 20). Contemporary reports now describe BWF clusters in high-transmission regions of East, Central and West Africa, with children constituting over 80% of cases [15–17]. For example, in Eastern Uganda, 12% of paediatric severe malaria admissions had BWF associated with mortality rates exceeding 15% [18, 19]. This distribution of BWF correlates with known drivers of high *P. falciparum* transmission intensity.

Despite the significant implication of BWF, reliable data on the true burden, distribution, and consequences of BWF in children across SSA remain fragmented and poorly quantified. Recent studies underscore BWF's complex aetiology, implicating interactions between host genetics, malaria treatment practices, and regional transmission dynamics [22–24], however, major inconsistencies persist. Firstly, while intense *P. falciparum* transmission correlates with BWF incidence, the roles of host genetics such as G6PDd, drug triggers and immune mechanisms are poorly defined. Notably, recent studies conflict on G6PDd's role, with Ugandan and Nigerian cohorts showing no significant association (20, 21). Furthermore, the coincidental re-emergence of BWF concurrent with the rollout of ACT has reignited debates over potential drug-specific triggers. Secondly, the clinical management of BWF lacks standardization such that adjunct therapies such as corticosteroids are applied empirically without robust evidence or consensus guidelines (22, 23).

Therefore, this scoping review aimed to systematically map the existing literature on BWF among children in SSA. Specifically, it aimed to describe the prevalence, incidence, and geographical distribution of BWF; characterize its clinical features and diagnostic approaches; identify risk factors; evaluate management strategies and associated outcomes. Consolidating this evidence will establish a cohesive framework for BWF management through informed clinical guidelines, and targeted interventions in malaria-endemic areas and prioritize research into genetic and mechanistic drivers.

Methods and materials

Protocol and registration

This scoping review followed the methodology framework proposed by Arksey and O'Malley (24) with enhancement by Levac et al (25). The scoping review protocol was registered with open science framework (OSF) https://doi.org/10.17605/OSF.IO/QNPKV, published(26) and adhered to the PRISMA-ScR reporting standards (supplementary file 1).

Patient and public involvement statement

No patients or members of the public were involved in the design, conduct, reporting, or dissemination plans of this scoping review. The study synthesised data exclusively from previously published literature and did not generate new individual-level data; therefore, direct patient or public involvement was neither appropriate nor feasible.

Eligibility criteria

We defined eligibility for this scoping review using the PCC framework (Population, Concept and Context).

Population

We included studies reporting on children aged 0-18 years with BWF. Studies without a specific focus on BWF or those exclusively reporting on adults were excluded.

Concepts

The key concepts of interest in this review included clinical features of BWF, such as passing dark urine, jaundice, and severe anaemia, associated risk factors, including genetic predisposition and treatment related risk factors. We also examined management strategies for BWF, such as malaria treatment, blood transfusions and other supportive treatments, and outcomes of BWF including AKI and mortality. We excluded studies whose findings were unrelated to these core concepts or focusing on other hemolytic conditions.

Context

The review geographical focus was limited SSA, a malaria endemic region accounting for the highest burden of disease globally, especially among children. We excluded studies reported outside this region to ensure contextual relevance to the review objectives. Within SSA, we considered variations across countries and sub-regions, including east, west, central, and southern subregions.

Study designs

We included a range of study designs including randomised controlled trials (RCTs), observational studies (cohorts, case control and cross sectional) and case series to capture diverse evidence on childhood BWF. In addition, to peer reviewed articles, we included relevant grey literature to ensure a comprehensive inclusion of literature, especially in areas where published research is limited.

Search strategy

Information sources

The search for this review was conducted across six databases, including PubMed (primary database), Embase, the Cochrane Library, CINAHL, PsycINFO and web of science. In addition, to the databases search, we searched relevant grey literature including conference proceedings, theses, dissertations, WHO reports and clinical trials registries (PACTR, clinicaltrials.gov).

Search terms

We systematically searched PubMed, Embase, the Cochrane Library, CINAHL and PsycINFO. Grey literature sources included WHO reports, conference proceedings and clinical trials registries. The search string was developed using a combination of Medical Subject Headings (MeSH terms), synonyms, and search filters tailored to each database. MeSH terms such as “Blackwater fever,” “Haemoglobinuria,” and “Quinine hemolysis” were pivotal to the search, Alternative terms and synonyms, including “dark urine malaria,” “malaria hemolysis,” and “severe malaria syndromes” were incorporated to enhance broadness and inclusivity of the search. Search filters were applied to include only studies involving “children” and populations in “Sub Saharan Africa” (see full syntax for the 6 databases in the supplementary file 2).

Search process

The search strings were constructed iteratively by a multidisciplinary team of malaria experts POO, RI, SK, RN and a health librarian, GA. This team refined the search terms and adapted them to syntax and indexing requirements of each of the six databases. To ensure precision and consistency across the six databases, tools such as MeshMate and polyglot search translator were used.

Supplementary search

To augment the six database searches, additional strategies were utilised including, manually screening the reference lists of all included studies, conducted backward and forward citation analyses using tools

such as CitationChaser (27), and consulted authors and experts in malaria.

Timing and coverage

The search was done on 12/08/2024, covering the databases from inception to the search date. There was no language restrictions applied to the search thereby capturing a broad range of relevant studies.

Study selection

This review utilised a multistage study selection process including title and abstract screening, full text screening, citation searches and trial registry screening. At each stage, at least two authors conducted the screening to ensure consistency and to minimise bias. We used nested knowledge tool (28) for this multistage screening process. This tool provides a structured environment for reviewers to independently screen studies and collaborate on resolving disagreements thus facilitating the efficient management of records, resolution of conflicts and the documentation of decisions.

Title and abstract screening

Two authors CN and GP independently screened titles and abstracts of all retrieved records to assess their eligibility against the predefined study inclusion and exclusion criteria. Each record was reviewed by the two authors and any disagreements were resolved by consensus or if necessary, by refereeing to a third author, POO for final adjudication.

Full text retrieval and screening

The full text articles of potentially eligible studies were retrieved by GA. The full texts were then independently screened by MN and to confirm inclusion using the study eligibility criteria, focusing on an in-depth assessment of the relevance of the population (children), geographical setting (SSA) and the study concept (BWF). Again, any disagreements were resolved by consensus or if necessary, by refereeing to a third author, RI for final adjudication.

Citation searches

Two authors DA and PO conducted backward and forward citation searches, to identify additional studies besides the one from the database search. The reference lists of included studies were manually reviewed, and citation tracking was done to identify relevant studies that might not have been captured by the database search.

Trial registry screening

FO and CN searched the trial registries including clinicaltrial.gov and PACTR for ongoing or unpublished studies that qualify for inclusion.

A detailed list of all excluded studies after full text screening with the reasons for exclusion is provided in the appendix (supplementary file 4)

Data charting process

Firstly, we developed a data charting form and piloted it on 5 studies to refine its clarity and applicability. Data charting was conducted independently by two authors GP and CN. Any disagreements or discrepancies during the charting process were resolved through consensus among the authors. Data was charted using a standardised template capturing: i) study characteristics (title, authors, year of publication, DOI, country of study, study design), ii) Study participant characteristics (age, sex, sample size), iii) epidemiology metrics (prevalence, incidence, geographical distribution), iv) clinical features (eg passing dark urine, jaundice, pallor) and diagnostic methods (clinical diagnosis or laboratory diagnosis), v) Risk factors (genetic predispositions like G6PDd, treatment-related risk factors like quinine ingestion), vi) management strategies (eg blood transfusions and other supportive managements like dialysis, steroids) and vii) outcomes (mortality, AKI). The charted data was managed using nested knowledge and Microsoft excel. Cross-checking of the charted data was done for a subset of the studies to ensure accuracy.

Risk of bias assessment

We did not perform a formal assessment of the quality of included studies as pre-specified in the study protocol. However, where relevant, the potential biases and methodological limitations of the included studies were highlighted descriptively during the data synthesis process to provide context for the findings.

Synthesis of results

We conducted data synthesis using a narrative approach to map the evidence landscape of childhood BWF in SSA. The charted data were organised into prespecified categories (epidemiology, clinical features, risk factors, management strategies and outcomes) and further stratified the data by age group (<5 years and ≥5 years) and geographical sub-regions (east, west, central, southern). The narrative summaries identified recurring patterns and inconsistencies in the charted data, supplemented by quantitative descriptors to document the prevalence estimates and risk factor frequencies. We categorized evidence gaps systematically using what/where/when/who/how framework. We explored heterogeneity in study designs and reporting with conflicting findings documented transparently. Results were visualised through summary tables.

Dealing with missing data

To deal with missing data, we directly contacted the investigators or study sponsors via email communication and follow up reminders to request for the missing data. Where the missing data could not be obtained, we documented these gaps transparently and noted the potential impact during the data synthesis process and interpretation of findings.

Subgroup and sensitivity analysis

Since this was a scoping review, we did not perform a formal subgroup or sensitivity analysis. However, the findings were stratified descriptively to explore the variations across different subgroups such as age group (<5 years and ≥5 years) and geographical setting. While we did not do any formal sensitivity analysis, patterns in our findings were carefully examined to identify gaps or inconsistencies thus providing a foundation for future research.

Software and reproducibility

Analyses were executed in R 4.3.2 (RStudio 2023.12, Ubuntu 22.04). Core packages: *readxl 1.4.3*, *janitor 2.2.0*, *dplyr 1.1.4*, *PRISMAstatement 1.0.1*, *ggplot2 3.5.1*, and *yaml 2.3.8*. The exact library state is snapshotted in session_info.txt. All code, raw data, and figures are tracked in a public GitHub repository (https://github.com/gpaasi/childhood-blackwater-fever-scoping-review). Every commit triggers a GitHub Actions workflow that (i) installs the declared packages, (ii) reruns parse_included_studies.R and generate_prisma_flow.R, and (iii) verifies that included_studies_clean.csv and figure1_prisma_flow.png are regenerated without error. A frozen copy of this workflow (release v1.0.0) is archived on Zenodo via https://doi.org/10.5281/zenodo.15647335. All materials are licensed CC BY 4.0, ensuring unrestricted reuse with attribution.

Results

Selection of included studies

A systematic search across six databases (PubMed, Embase, Cochrane Library, CINAHL, Ovid MEDLINE, and Web of Science) yielded 329 records. After removing 155 duplicates, 174 records underwent title and abstract screening. Of these, 120 were excluded due to irrelevance to Plasmodium falciparum malaria with BWF (n=48), non-pediatric populations (n=21), non-human or in vitro studies (n=7), editorials/opinions (n=10), case reports with fewer than five patients (n=14), protocols/abstracts (n=9), missed duplicates (n=6), or focus on other malaria complications (n=14). Following screening, 54 full-text reports were sought for retrieval, with one unavailable, leaving 53 for eligibility assessment. Of these, 29 were excluded: case reports with <5 patients (n=6), editorials/opinions (n=3), protocols (n=1), non-BWF focus (n=8), adult-only populations (n=4), in vitro studies (n=1), insufficient data (n=2), or lack

of alignment with review objectives (n=4). This resulted in 24 studies eligible for inclusion. Complementary searches via citation tracking, grey literature, and expert consultation identified 59 additional records. After screening, 12 full-text reports were assessed, with 10 excluded (adult studies (n=2), duplicates (n=3), non-BWF focus (n=3), editorials (n=1), protocols (n=1)), yielding two eligible studies. In total, 26 studies met the inclusion criteria and were incorporated into the systematic review (Figure 1).

Temporal trend

Figure 2 below shows the number of publications on BWF over the years 1969 to 2025. From 1970 to 2000, the number of publications remained relatively low, with occasional increases in some years. In 2013, there was sudden peak in number of publications on BWF, followed by a notable rise in publications from 2020 onwards especially in between 2022 and 2023.

Characteristics of included studies

Twenty-six studies conducted between 2003 and 2024 were included in this review. Majority of the studies, 15 (57.7%) were conducted in Uganda (8, 19, 20, 29-40) while 7(26.9%) were conducted in Democratic Republic of Congo (DRC) (7, 18, 41-45). Single studies were conducted in Nigeria (21), Burundi (17), Tanzania (46), Cote Ivoire (47) and Togo (48). Most studies employed observational study designs, including prospective cohort designs (n=10, 46.2%) (7, 8, 19, 21, 31-34, 38, 45, 47, 49) , retrospective cohort designs (n=6, 23.1%) (7, 20, 29, 35, 41, 48), case control designs (n=5, 19.2%) (18, 21, 29, 42, 43), one case series (17) and three randomised controlled trial (36) with two being secondary analyses. All studies were primarily hospital based. See detailed table of included studies in supplementary file 3.

Study participant characteristics

The total number of participants across the included studies was 23746, with sample sizes ranging from 9 participants (17) to 5425 participants (36). Out of the 23746 participants, 7836 (33%) had BWF, mostly children >5 years of age (18, 29, 32, 35, 43-45). In Uganda, with 76.8% of the cases >5 years and 81.4-94.8% of the cases >5 years in DRC. The mean age ranged from 2.1 years (19) to 8.62 years (18) with variations by regions; cohorts in Uganda were younger with (mean 1.9 - 6 year) (8, 19, 20, 29, 31), while studies in DRC included older children (mean 8.2 - 8.62 years) (7, 18, 42, 43). In Nigeria, 76.8% of the cases were children under 5 years of age with a median age of 52.5 months (21). The gender distribution was nearly equal across the included studies except for a slight male predominance in some cohorts in Uganda with 54.2 - 64% of the cases happening in males (8, 20, 31, 32, 35) and a study in Burundi where all the cases were male (17).

Epidemiology

Geographical distribution

The geographical distribution of BWF among children in SSA revealed a concentration of cases in East and central Africa, especially in Uganda and DRC (Figure 3). Together these countries reported 7417/7836 (94.7%) cases of BWF in children, with Uganda accounting for about 94.8% (n=7033) of the cases. In Uganda, the highest burden was observed in East Uganda (8, 19, 20, 29-35). DRC contributed 384 (5.2%) cases mostly observed in Kinshasha, with studies reporting BWF in older children and emphasising its association with AKI (7, 18, 42-45). Outside these regions, small case clusters have been reported in Burundi (17), Nigeria (21), Cote d'Ivoire (47) and Togo (48). Notably there were no reports from North and Southern Africa.

Prevalence and incidence

The prevalence of BWF varied across settings ranging from 4.4 to 52.7% (32, 36). A hospital-based study in Eastern Uganda reported the highest prevalence, 52.7% among 300 children with severe malaria (32). Other studies in this region, for instance, Olupot-Olupot et al. (2017) reported high prevalence rates of BWF at Mbale (14.5%) and Soroti (21.8%) among 3170 children at these tertiary hospitals (20) while Namazzi et al. (2024), also reported a prevalence of 31.5% in the same region (19). while in DRC, the BWF was reported in 25.3% to 33.3% of children with severe malaria (18, 44). Conversely, a lower prevalence rate of 4.4% was observed in a large multicentre clinical trial of 5379 children with severe malaria across eleven African countries to compare the efficacy of artesunate vs quinine; BWF prevalence in the artesunate arm was 1.2% while in the quinine arm it was 0.7% (36). Similarly, the incidence of BWF varied substantially by regions, 19.1% incidence among 251 children with severe malaria was observed in Ibadan, Nigeria (21). In eastern Uganda, district level incidence rates varied from 1.2 to 5.0 cases per 10000 children, peaking in Soroti district in eastern Uganda (29), while in Burundi the incidence was 11.5 cases/100000/year (17).

Risk factors

Genetic predispositions

Studies have reported contrasting findings about the association of G6PDd and BWF among children. For instance, Namazzi et al. (2024) reported that G6PDd African allele (A-) was significantly associated with BWF. In the study cohort, the G6PDd African allele (A-) was present in 16.8% of male children with severe malaria. Among these boys, G6PDd was significantly associated with increased levels of circulating immune complexes (cIC) ($p = 0.01$). Mediation analysis indicated that this genetic deficiency contributed to recurrent BWF through its effect on cIC levels. Specifically, elevated cIC levels were

strongly linked to BWF, with an adjusted odds ratio of 5.21 (95% CI, 2.06-13.18; p < 0.0001) for the occurrence of BWF and an adjusted incidence rate ratio of 7.66 (95% CI, 2.62-22.45; p < 0.0001) for readmissions due to BWF (19). Contrary to this, Olupot-Olupot et al. (2017) reported that there was no significant difference in the prevalence of G6PDd between the BWF cases (15.6%) and the controls (11.9%) (20). Similarly, Ajetunmobi et al. (2012) reported no association between G6PDd and haemoglobinuria in Nigerian children (21). Furthermore, Bodi et al. (2013), reported a higher prevalence of G6PDd in non-BWF controls of 39.5% compared to BWF cases (18.6%) though the difference was not statistically significant (18). On the other hand, some genetic predispositions reported to be strongly associated with BWF. For instance, a case-control study of 129 Congolese children (43 with BWF and 86 with uncomplicated malaria (UM)), allele and genotype frequencies of the MBL2 gene were examined. The ancestral MBL2A allele was found at a frequency of 76.7% in BWF patients versus 61.0% in UM patients (OR, 2.67; 95% CI, 0.87-8.29; p = 0.079), although this difference did not reach statistical significance. In contrast, the MBL2C allele was less frequent in BWF patients (18.6%) compared with UM patients (29.1%; p = 0.853), and no MBL2-D allele was detected. Genotypic analysis revealed that the homozygous AA genotype occurred significantly more often in the BWF group (72.0%) than in the UM group (50.0%). Moreover, heterozygous A0 genotypes (comprising AB and AC) were significantly over-represented among UM patients, conferring a protective effect against BWF (OR, 0.21; 95% CI, 0.06-0.78; p = 0.019) (42). Relatedly, Bodi et al. (2018) reported increased levels of malaria IgG1 antibody levels in children with BWF. In this case-control study involving 129 Congolese children (43 with BWF and 86 with uncomplicated malaria (UM)), malaria-specific IgG1 levels were quantified by ELISA. The geometric mean IgG1 level in children with BWF was 1.95 (95% CI, 1.55-2.44), which was significantly higher than the level of 1.19 (95% CI, 0.98-1.43) observed in the UM group (p = 0.002). Importantly, no significant linear correlation was found between patient age and IgG1 levels (p = 0.349), indicating that the elevated IgG1 response in BWF is independent of age (43). Other protective genetic traits reported included the sickle cell trait and α-thalassaemia. Olupot-Olupot et al. (2017) reported that homozygous α+thalassaemia and sickle trait (HbAS) offered protection against BWF with odds ratios of 0.53 (p=0.09) and 0.26 (p<0.001) respectively while HbSS was associated with higher risk of BWF (OR=0.489, p<0.001) (20).

Antecedent antimalarial treatment

Quinine use was identified as a significant risk factor for BWF, with studies in DRC and Cote d'Ivoire, reporting 78.5 to 95.3% of BWF cases occurred in individuals exposed to quinine before symptom onset (17, 18, 41-44, 47). The risk from quinine exposure corresponded to adjusted odds ratios ranging from 50.19 (95%CI 10.75 -234.42) to 57.33(95% CI 11.65 -282.08) (18, 42). Conversely, in a large multicentre trial involving eleven African countries, BWF was rare in both treatment arm; 1.2% of the 2591children in the artesunate arm compared to 0.7% of the 2597 children in the quinine arm, with the odds ratio for developing BWF being 1.69 (95%CI 0.94-3.05; p=0.076) (36). Although Namazzi et al. (2024) and Olupot et al. (2017) reported that the introduction of ACTs and intravenous artesunate coincided with an increase in BWF in the region, these observations are largely anecdotal (19, 20).

Environmental factors

Geographical and seasonal variations were observed in the incidence of BWF among children in SSA. Olupot-Olupot et al. (2017) in a large multicentre trial involving three countries (Uganda, Kenya and Tanzania) reported a notable geographical variation in the frequency of BWF, with eastern uganda, a high transmission region demonstrating a 3.4-fold greater BWF incidence than the low transmission areas. Within Uganda, majority of the BWF cases were reported at Soroti (21.8%) and Mbale (14.5%) tertiary hospital in eastern Uganda compared to 11.5% of the cases at Lacor hospital in Gulu, northern Uganda, and 6.2% in Mulago hospital in the central region. While outside Uganda, 0.5% of the cases were reported in Kilifi Kenya and 2% of the cases in Teule, Tanzania (20). In addition, the incidence of BWF correlated with the malaria transmission peaks. For instance, in DRC, 88.4% of the 129 BWF cases occurred during the rainy season (OR=5.22, 95% CI 1.87-14.56) (18).

Clinical features

Dark urine also described “tea-coloured urine,” “coca cola urine” was the hallmark clinical feature that was consistently reported across studies, with up to100% of the cases presenting with dark urine in several cohorts (8, 18-20, 31, 35). Other common symptoms included jaundice reported in 22.7 to 100% of the cases(7, 8, 18-21, 31, 32, 41, 44, 45, 47), pallor reported in 26.1% to 100% of the cases (7, 18, 21, 29, 35, 45) and fever reported in 53% to 96.6% of cases (7, 18, 29, 35, 41). Gastrointestinal symptoms such as vomiting was reported in 18.1% to 79.7% of the cases (7, 21, 29, 31, 32, 44, 45) and abdominal pain in 12.7% to 73.4% of the cases (29, 32, 44). In addition, prostration was reported in 41.4 % to 94.6% (35, 44, 45) , hepatomegaly in 70.3% to 92.3% (7, 45) and oliguria in 66.6% to 85.3% of the cases (7, 41, 44, 45). Severe anaemia (Hb<5 g/dL) was present in 23.7% to 77% of the cases (19, 20, 32, 44).

Diagnosis

The diagnosis of BWF among children in the included studies was primary by clinical criteria with the presence of dark urine or “tea-coloured urine” or “coca cola coloured urine” being the hallmark diagnostic feature (8, 20, 29-32, 34, 35). Notably, several studies in eastern Uganda that used only the clinical criteria for diagnosis did so with the aided of the Hillmen urine colour chart (HUCC) to grade the color of urine with a grade >5 indicating BWF (Figure 3) (8, 20, 32, 34, 35). Other studies employed both clinical criteria and laboratory criteria of detection of haemoglobinuria (18, 19, 41, 42, 45, 47-49). In majority of the studies, that used both the clinical and laboratory criteria, parental reports of dark urine were used for initial diagnosis, for instance, a study in eastern Uganda reported an 80% agreement between the parental observations and laboratory confirmation of haemoglobinuria using urine dipsticks (19). Laboratory confirmation of haemoglobinuria was mostly done using urine dipstick tests to detect free hemoglobin in urine (18, 33, 45, 47, 49), however, advanced diagnostic techniques such as spectrophotometric quantification of urinary hemoglobin were rarely used (21).

Figure 3. Use of the Hillmen urine colour chart to diagnose BWF. At admission, the patient/guardian was first asked to recall and match the colour of urine passed by their child on the day of admission to a colour on the HUCC. If available, urine was collected from the child using paediatric urine collection bags before it was transferred into the urine collection bottle. Then the attending study clinician then matched the urine colour to the corresponding score on the HUCC scale. Children with clinician- witnessed urine or patient/guardian matched colour of urine corresponding to HUCC >5 on the chart were confirmed to have BWF.

Evidence of malaria parasitaemia

Low malaria parasitaemia was a consistent finding among children with BWF, with several studies reporting lower parasite densities in BWF cases compared non-BWF controls. For example, Bodi et al. (2013) and (2020) reported that majority of the BWF cases 78% presented with low parasitaemia (<500 parasites/μL), significantly higher compared to non-BWF cases with uncomplicated malaria (51.8%, p=0.005) (18). Similarly, Olupot-Olupot et al. (2017), reported a lower geometric mean concentration of plasmodium falciparum histidine-rich protein 2 (pfHRP2) compared to non-BWF controls (200ng/mL vs 613ng/mL; p<0.0001), with parasitaemia being less commonly detected by blood slide or pfHRP2 rapid diagnostic tests among BWF cases compared to non-BWF controls (60.4% vs 74.0%; p<0.0001) (20). A study by Opoka et al. (2020), reported low parasite densities among children with severe anaemia and BWF (SA+BWF) compared to children with severe anaemia without BWF (SA) that is children with SA+BWF had a mean parasite density of 43826 parasites/μL compared to 107,618 parasites/μL in children with SA (p=0.04) (8). Although there were differences in parasite densities, the prevalence of parasitaemia was comparable between the groups that is 38% in SA+BWF vs 36.9% in SA; p=0.852. In a recent study reported similar findings where among 377 children hospitalized with severe malaria, BWF cases had a mean parasite density of approximately 98,000 parasites/μL, which was lower than the average for the cohort (~136,000/μL) (38). other studies reporting low parasitaemia included a study in Nigeria found a lower geometric mean parasite count in patients with haemoglobinuria compared to controls, but the difference was not statistically significant (8960.9 vs 9209.6 parasites/μL) (21), while a study in Burundi reported scanty or absent parasitaemia among BWF cases (17).

Outcomes

Mortality

The mortality associated with BWF varied across studies influenced by settings and clinical severity, with studies in Uganda reporting lower mortality rates ranging from 0.5% to 14.1% (8, 20, 29, 31, 35). For instance, a study of 4,913 cases of BWF in eastern Uganda, there were 26 deaths recorded resulting in a case fatality rate of 0.5% (29). Similarly, among 920 children admitted with BWF, the overall case fatality rate was 3.2% (29/920), with 69% (20/29) of the deaths occurring within the first 48 hours after

admission to 3.2% (35). Opoka et al. (2020) in a prospective study of 279 children, observed a post discharge mortality of 14.1% among the children with severe anaemia and BWF compared to 4.8% in the severe anaemia without BWF ($p<0.05$) (8). A comparable in-hospital mortality rate was observed between BWF cases and non-BWF controls (2.4% vs 3.0%) by Conroy et al. (2022) (31). Similarly, Olupot-Olupot et al. (2017) observed a comparable cumulative 28-day mortality rate of 12.3% among BWF cases and non-BWF controls (9.9%). Conversely, studies done in the DRC, reported higher mortality rates, for example Bodi et al. (2014) reported 22.2% mortality among 63 BWF cases with AKI (7) while Kanuanunua et al. (2013) reported mortality rate of 12.6% among 87 children with BWF-associated AKI (45).

Complications

Several complications were associated with BWF, with AKI and severe anaemia being the most prevalent. AKI was the most life-threatening BWF-associated complication, affecting 16.2% to 90.6% among BWF cases in DRC (18, 45) while in Uganda, Olupot-Olupot et al. (2017) reported features of renal dysfunction among children with BWF including elevated blood urea nitrogen (BUN) in 65.8% of the cases and oliguria in 66.6% of the cases (20). Similarly, in a cohort of 999 children hospitalized with acute febrile illness a history of BWF on admission was independently associated with AKI, with an adjusted odds ratio of 2.18 (95% CI: 1.15-4.16) (31). Severe anaemia (Hb<5 g/dL) was reported in 77% of the BWF cases [Olupot-Olupot], requiring blood transfusions in 88.7% of the BWF cases, with 33% of these requiring multiple blood transfusions (20). Furthermore, metabolic and electrolyte imbalances were notable complications of BWF, with metabolic acidosis (pH <7.2) observed in 97.4% among 39 BWF cases, hyponatremia in 74.3% and hyperkalaemia 51.2% (7) while Kunuanunua et al. (2015) found metabolic acidosis of 54.2%, hypernatremia of 38.5% and hyperkalaemia of 36.5% (44).

Hospitalisation and readmission patterns

Children with BWF experienced significantly worse in-patient and post discharge outcomes than those without BWF. Paasi et al. (2022) reported that 27.3% of admitted BWF cases had prolonged hospital stay (>5 days) (35). In another cohort, 54.4% of children with severe anemia (SA) and BWF were readmitted within six months, compared with 41.7% of SA children without BWF. In addition, the presence of BWF was associated with a 68% increased risk of readmission (adjusted HR = 1.68; 95% CI: 1.1-2.5). Moreover, a repeat episode of BWF occurred in 50-60% of the readmissions, typically occurring within the first three months after discharge (8). Relatedly, increased circulating immune complexes (cIC) at admission strongly predicted the risk of readmission among children with BWF (aIRR: 7.66; 95%CI: 2.62-22.45) (19).

Management

Antimalarial treatment

The primary antimalarial regimen for the management of BWF in children included artemisinin-based therapies, in particular intravenous artesunate, followed by the use of oral artemisinin-combination therapy (ACT), according to national guidelines for malaria treatment (19, 33). A shift away from quinine-based regimens to artemisinin-based regimens was well documented by studies such as Kunuanunua et al. (2013) and Bodi et al (2014) reported immediate stoppage of quinine following BWF diagnosis and switched treatment to intravenous artemether or artesunate (7, 45). Similarly, Aloni et al (2012) and Gobbi et al (2005) reported the use of parental artemether after stopping quinine treatment (17, 41).

Supportive treatments

Blood transfusion for the treatment of severe anaemia (Hb<5g/dL) caused by BWF was the most common supportive treatment reported across studies. Olupot-Olupot et al. (2017), reported 88.7% of the BWF cases received blood transfusion compared to 45.1% of the non-BWF controls, with 33.3% needing multiple blood transfusions (20). Opoka et al. (2020) reported that children with severe anaemia and BWF were more likely to require a blood transfusion than those with severe anaemia alone (59.8% vs 37.0%) (8). Similarly, Namazzi et al (2024), reported that 99.6% of children with severe anaemia associated with BWF received a blood transfusion, with a mean of 0.86 transfusions per child (19). Although blood transfusions were crucial in management of severe anaemia due to BWF, there were notable challenges in its timely availability as noted by Paasi et al. (2022) who reported that only 38.5% of the 13 BWF patients with severe anaemia who died had received a blood transfusion within 48 hours (35). On the other hand, the management of complications such as AKI commonly involved conservative management, including fluids and electrolyte correction and diuretics while peritoneal dialysis was preserved for the severe cases (45). Daubrey-Potey et al. (2004) reported that 47% of the patients with BWF-associated AKI required peritoneal dialysis (47) while Bodi et al. (2014), reported that 20 with BWF received peritoneal dialysis (mean 3 sessions/patient) (7), yet in a similar setting, among the 7 BWF patients that developed AKI, only 2/7 received peritoneal dialysis and the remaining 5 faced delays or denials of peritoneal dialysis due financial constraints leading to death in 3/5 patients (18). Other supportive treatments included use of antibiotics and corticosteroids among children admitted with BWF. For instance, Paasi et al. (2022) revealed that antibiotic use was significantly more common in BWF cases with prolonged hospitalisation: 62.6% of BWF cases admitted >5 days received antibiotics, compared with 54.4% in those with shorter hospital stays ($p = 0.027$). In contrast, steroid use was similar between the two groups, with 28.4% of BWF cases admitted with shorter hospital stays and 31.1% of those with prolonged hospitalisation receiving steroids ($p = 0.427$) (35).

Discussion

We synthesised evidence from 24 studies in this scoping review to characterise the resurgence of BWF, among children in SSA elucidating its clinical burden, and systemic challenges of BWF, offering critical

evidence into its epidemiology, pathogenesis, and management.

This scoping review highlights a pronounced geographical concentration of BWF cases among children in SSA, with ~ 94% of reported paediatric BWF cases in recent literature coming from Uganda and the DRC (18, 20). In particular, eastern Uganda and parts of DRC have experienced notable BWF upsurges, often corresponding to seasonal malaria peaks during the rainy seasons (18). For example, an analysis of a multicentre severe malaria trial found an exceptionally high prevalence of BWF in eastern Ugandan sites up to ~ 15–22% of children with severe febrile illness compared to other regions (20). Similarly, a study in DRC reported that 88% of BWF episodes occurred in the rainy high-transmission season (18). This geographic overlap correlates with areas of intense *Plasmodium falciparum* transmission and prolonged historical reliance on quinine for malaria treatment, suggesting synergistic roles of parasite exposure and drug use in BWF epidemiology (17, 18, 20).

The resurgence of BWF in SSA, particularly in Uganda and the DRC, mirrors historical patterns observed during the pre-ACT era, when BWF emerged as a severe complication of *Plasmodium falciparum* malaria. BWF, initially observed in non-immune European expatriates in Africa and Asia during the early 20th century, was historically associated with quinine use for malaria treatment and represented a significant cause of mortality in malaria-endemic regions (15, 47, 50). Following the adoption of chloroquine as first-line therapy in the 1950s (15, 51), BWF incidence declined sharply, with cases remaining rare throughout the chloroquine era (1950–1990) (15–17). However, the recycling of quinine and other amino-alcohol antimalarials due to chloroquine resistance (15, 52), alongside the rollout of ACTs in the 2000s, coincided with BWF re-emergence in Africa, reigniting debates about drug-specific triggers (18–20). Notably, quinine's role as a BWF trigger endures despite declining use as it remains strongly implicated in BWF pathogenesis (12–14), with hemolytic risks extending to related amino-alcohol drugs like halofantrine(15, 53), mefloquine(54, 55), and lumefantrine (56, 57). In contrast, ACTs show no direct association with BWF. Although few isolated cases of ACT related BWF have been reported (17, 22, 56, 58, 59), a large multicountry trial found no significant difference in BWF incidence between artesunate-based regimens and quinine (36), suggesting ACTs are unlikely primary triggers. Nonetheless, pharmacovigilance should remain critical in high-risk regions, where genetic and environmental factors may interact unpredictably with antimalarial therapies.

The role of G6PDd in BWF pathogenesis remains contentious. The conflicting associations of G6PDd with BWF that is protective in DRC (18) but was associated with a three-fold increased risk of BWF and associated with readmissions in in Ugandan children (19), however, other studies in Nigeria and Uganda found no significant association (20, 21). This discrepancy may reflect population-specific allele frequencies or methodological differences in phenotyping (enzyme activity vs. genotyping). The African A- allele, which is prevalent in SSA, results in moderate G6PD enzyme deficiency, retaining approximately 10–60% of normal activity. While this partial deficiency often remains clinically silent, it can exacerbate oxidative stress during hemolytic crises, such as those triggered by certain drugs, or malaria. In contrast, the Mediterranean variant rarely found in SSA is associated with a much more severe deficiency, typically classified as Class I, with less than 1% residual enzyme activity. This form is linked to chronic

nonspherocytic hemolytic anemia and poses a significantly higher risk of spontaneous and drug-induced hemolysis (60).

Emerging evidence implicates immune dysregulation as a critical mediator in the pathogenesis of BWF. Findings suggest BWF arises from an immune overreaction where sub-optimally immune children generate IgG1-rich immune complexes involving parasite antigen PfEMP1 that over-activate complement and lead to recurrent hemolysis disproportionate to parasite load. The hallmark low parasitaemia in BWF cases (8, 18, 21, 42) diverges from classic severe malaria and supports an immune-driven aetiology suggesting that an exaggerated host response rather than parasite burden alone causes the hemolytic crisis (43, 61). Similar patterns are seen in post-artesunate delayed hemolysis (PADH), where parasite clearance unmasks underlying red cell fragility (62). However, unlike PADH, BWF often occurs *during* acute malaria, suggesting distinct triggers. Evidence of immune dysregulation is shown in children with BWF who have an immune profile resembling malaria-naïve patients, with abnormally high levels of IgG1 antibodies against malaria antigens and a failure to develop the usual IgG3-mediated immunity seen children with BWF (61). These IgG1 antibodies called “hemolysins” form immune complexes that bind complement component C1q, triggering complement activation and massive intravascular hemolysis (61). Similarly, genetic susceptibility also plays a role as polymorphisms in the MBL2 have been associated with BWF. In particular, children with the MBL2 AA genotype (associated with high MBL levels) were at higher risk of BWF, whereas those with variant alleles (lower MBL activity) appeared protected (42). The hypothesis is that robust MBL complement activity in AA individuals may contribute to hemolysis by enhancing opsonization and clearance of both parasitized and non-parasitized RBCs, contributing to the intravascular hemolysis characteristic of BWF (61). Furthermore, the residual circulating immune complexes reported among children with BWF (19) perhaps sustain low-grade complement activation which in the presence of repeated malaria infections amplify immune complex formation, creating a self-reinforcing cycle of hemolysis that may lead to recurrent BWF episodes even with low parasitemia (8, 18, 21, 42). This aligns with the predominance of BWF in older children.

Diagnosing BWF remains fraught with challenges due to reliance on subjective clinical criteria, low parasitemia, and limited access to confirmatory tests. The widely used HUCC criteria lack specificity, as parental reports of dark urine show only 80% concordance with dipstick-confirmed hemoglobinuria, risking overdiagnosis (19). Low parasite densities further reduce the sensitivity of pfHRP2-based rapid diagnostic tests, which returned negative results in ≤ 50% of confirmed BWF cases due to insufficient parasite biomass (20). Innovations such as point-of-care haptoglobin assays or urinary hemoglobin spectrophotometry could improve diagnostic specificity (21), but these tools remain inaccessible in most endemic settings due to cost and infrastructure limitations. Thus, standardizing BWF diagnostic protocols such as validating HUCC against laboratory-confirmed cases are critical steps to reduce misdiagnosis.

BWF is associated with poor outcomes including inpatient mortality rates up to ~ 22% in African hospitals (18), far higher than typical severe malaria mortality (63). Notably, the higher mortality in DRC (22.2%) compared to Uganda (0.5–3.2%) underscores disparities in resource availability, particularly

blood transfusions and dialysis a finding consistent with studies linking AKI management delays to poor outcomes. BWF dramatically worsens the prognosis of severe malaria: for instance, children with BWF have about a 3-fold higher risk of death compared to those with severe malarial anemia alone (8). AKI, was frequently reported in up to 90% of paediatric BWF cases, contributing to 70% of deaths in the DRC, where limited dialysis access exacerbates outcomes. The high prevalence of AKI in BWF cases mirrors findings from adult studies in the 1990s but highlights a troubling shift toward pediatric vulnerability. Moreover, the development of chronic kidney injury is a concern as well, since repetitive renal insult can lead to renal scarring. Post-discharge outcomes of BWF are also poor as a Ugandan cohort study of children surviving an acute BWF episode found that 45–50% were readmitted at least once in the next 6 months, and the 6-month post-discharge mortality was significantly higher in the BWF group (7.5% overall, with BWF conferring a 68% relative increase in readmission risk) (8). Many children suffer recurrent BWF episodes in eastern Uganda, 68% of children with BWF had another severe illness or readmission within half a year (8). This recurrent episodes of BWF drives chronic morbidity, perpetuating cycles of transfusion dependency and healthcare utilization. These outcomes underscore the need for equitable AKI management protocols and long-term hematologic follow-up.

However, despite the significant clinical implication of BWF, major critical gaps persist in its management, including delayed blood transfusions, limited access to renal replacement therapy (RRT), and inconsistent adherence to artemisinin-based therapies, exacerbating mortality in resource-limited settings. Delays in transfusion and prohibitive costs of dialysis disproportionately affect outcomes (18, 35), while residual quinine use in regions like the DRC perpetuates BWF risk (7, 18, 35, 44, 45). Despite WHO guidelines prioritizing ACT, quinine remains widely used in the DRC due to stockouts and prescriber habits, increasing BWF incidence. Addressing these gaps requires urgent implementation of rapid transfusion protocols to prioritize BWF cases during blood shortages, dialysis subsidies to expand access in high-burden regions, and stricter enforcement of artemisinin-based treatment policies to eliminate quinine use.

Strengths and limitations

This scoping review synthesized paediatric BWF evidence across SSA, spanning six decades (1960–2021) and capturing diverse clinical contexts, across different settings and study designs and mapped historical and contemporary trends in BWF epidemiology, presentation, and management. The inclusion of multidisciplinary expertise during the review process minimized bias in study selection and interpretation. However, some limitations are noteworthy. Firstly, most included studies were retrospective or hospital-based, disproportionately representing severe cases treated at tertiary centers and excluding milder or fatal community-based episodes. Reliance on hospital data also precludes accurate estimation of BWF's true community burden, as prevalence figures reflect only hospitalized severe malaria cohorts. Heterogeneity in case definitions further complicates comparisons: some studies required laboratory-confirmed hemoglobinuria, while others relied on caregiver-reported dark

urine, introducing potential misclassification. Longitudinal data were sparse, with few studies tracking outcomes beyond acute hospitalization, limiting evidence into recurrence rates or long-term sequelae.

Future directions

This review underscores urgent priorities for advancing BWF research and clinical care. First, detailed genetic and immunological studies are essential to clarify host factors driving susceptibility, such as genetic polymorphisms or complement regulatory protein variants, and to characterize immune mediators such as cytokine profiles and autoantibodies during acute episodes. Second, systematic drug safety monitoring within malaria treatment programs could elucidate associations between antimalarial regimens and BWF risk, informing policy updates. Third, diagnostic innovation is critical: developing point-of-care assays for plasma free hemoglobin or urinary myoglobin could improve specificity, while validating standardized diagnostic criteria would reduce misclassification in research and surveillance. Fourth, prospective cohort studies tracking children post-BWF are needed to quantify recurrence rates, chronic kidney disease risk, and long-term hematologic outcomes. Finally, clinical trials evaluating adjunct therapies, such as corticosteroids for immune modulation or complement inhibitors to disrupt hemolysis, could address current evidence gaps in management. Addressing these priorities demands collaborative efforts across clinical, translational, and public health sectors to mitigate BWF's burden in endemic regions

Conclusion

This scoping review highlights the resurgence of BWF among children in SSA, driven by a complex interaction of immune-mediated processes, genetic susceptibility, and residual reliance on quinine in high malaria transmission regions. Recent pediatric clusters of BWF in Uganda, Nigeria, and the DRC have been linked to frequent AKI, multiple blood transfusions and case fatality rates exceeding 20%. Notably, these findings highlight critical gaps such as absence of consensus guidelines for acute management and recurrence prevention perpetuates poor outcomes, exacerbated by limited access to transfusions and renal support in these resource-constrained settings. Therefore, urgent priorities include robust surveillance to map BWF burden, studies clarifying pathogenesis, and trials evaluating context-appropriate interventions. Furthermore, strengthening healthcare capacity through accessible blood banks, dialysis units, and staff training must parallel research efforts to mitigate mortality. Lastly, integrating BWF into malaria control programs is imperative to address its neglect. This review calls for harmonized case definitions, longitudinal outcome tracking, and targeted policies to reduce disparities in care. Addressing these challenges will require multidisciplinary collaboration to transform BWF from a clinical enigma into a manageable component of pediatric malaria care, ultimately safeguarding vulnerable children in endemic regions.

Declarations

Ethics approval and consent to participate

This study was a secondary analysis of published peer-reviewed articles; no human subjects or identifiable data were involved.

Consent for publication

Not applicable.

Availability of data and materials

All data sources, analysis scripts, and supplementary files underpinning this review are openly accessible. The live, version-controlled workflow is hosted on GitHub at https://github.com/gpaasi/childhood-blackwater-fever-scoping-review, where readers can inspect the raw search strategies, screening logs, cleaned extraction tables, R scripts, continuous-integration configuration, and full project documentation. To ensure long-term preservation and precise reproducibility, an immutable snapshot corresponding to release v1.0.0 has been deposited on Zenodo via https://doi.org/10.5281/zenodo.15647335. Both the GitHub repository and the Zenodo archive are distributed under the Creative Commons Attribution 4.0 International licence, permitting unrestricted reuse, distribution, and adaptation provided appropriate credit is given.

Competing interests

The authors declare no competing interests, financial or otherwise, that could have influenced the study design, analysis, or reporting.

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Authors' contributions

All authors have made substantive intellectual contributions to the development of this manuscript. G.P conceived the scoping review scope, co-designed the search strategy across PubMed, Scopus, and grey literature with GA, and led thematic synthesis. P.O-O, SK, RI, RN IGM, DM supervised provided methodological oversight, and guided protocol alignment with PRISMA-ScR standards. M.N. and G.A co-screened titles/abstracts using predefined inclusion criteria, resolving discrepancies through consensus.

D.A and R.N conducted full-text reviews, with arbitration by P.O for contested articles. C.N and C.O extracted and charted data into structured templates, ensuring consistency, while F.A and J.A. supported data validation. F.O and G.P synthesized findings into thematic frameworks, with iterative refinement by C.N and G.P. All authors contributed to drafting and revising the manuscript, addressing three rounds of peer review feedback focused on methodological transparency, thematic coherence, and PRISMA-ScR adherence. Final approval followed rigorous appraisal of the narrative's alignment with the review's objectives.

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Figures

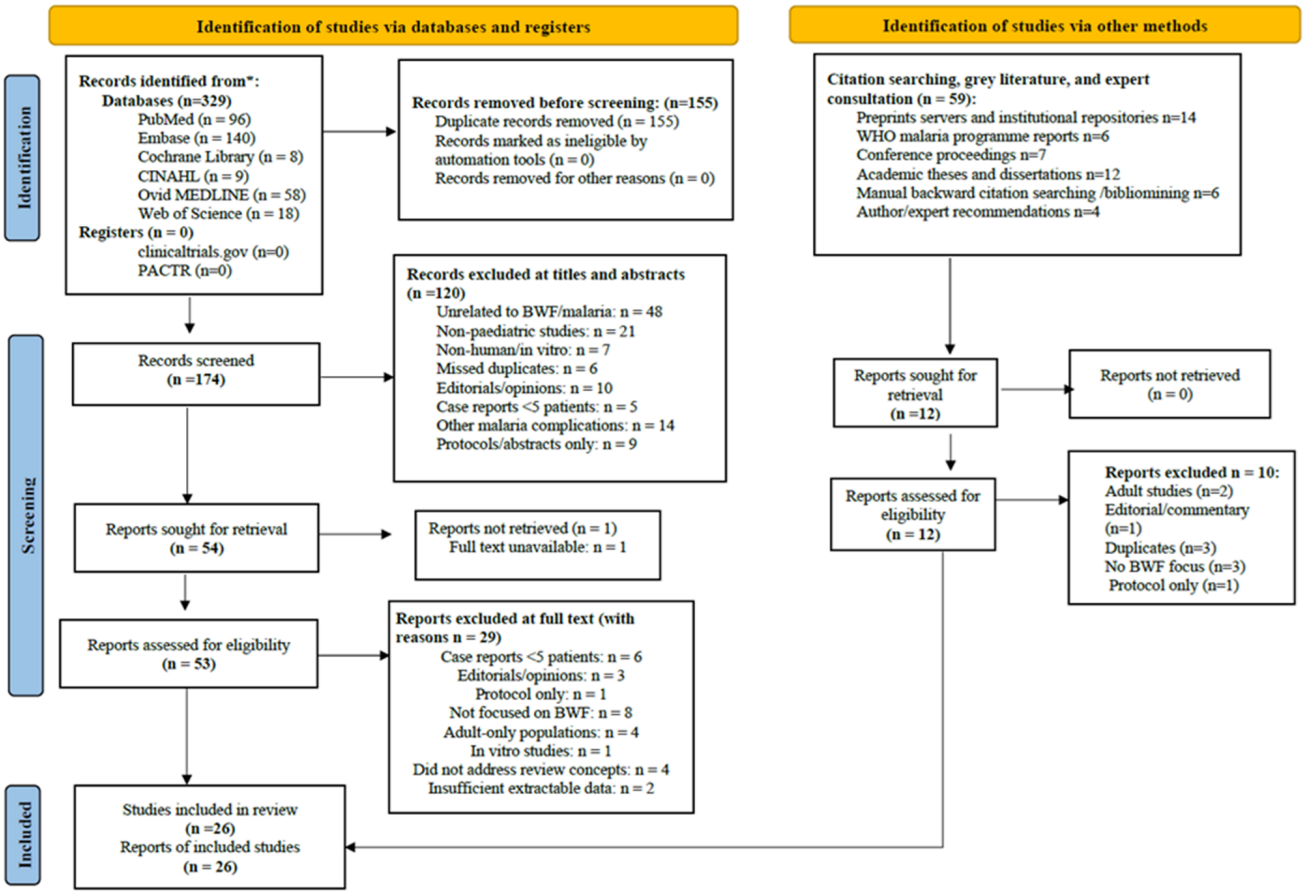

Figure 1

PRISMA flow diagram

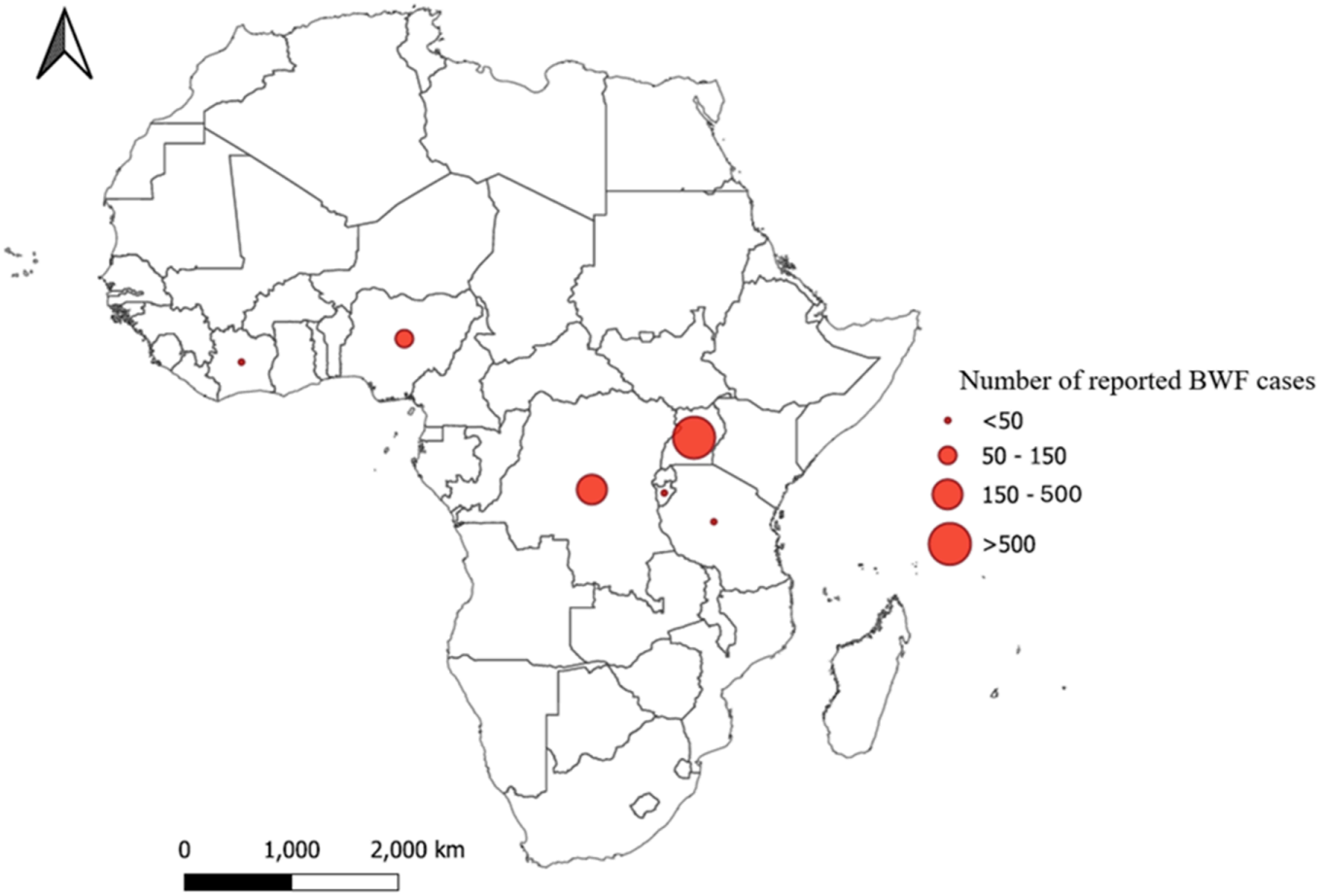

Figure 2

Temporal trend in the number of publications of blackwater fever

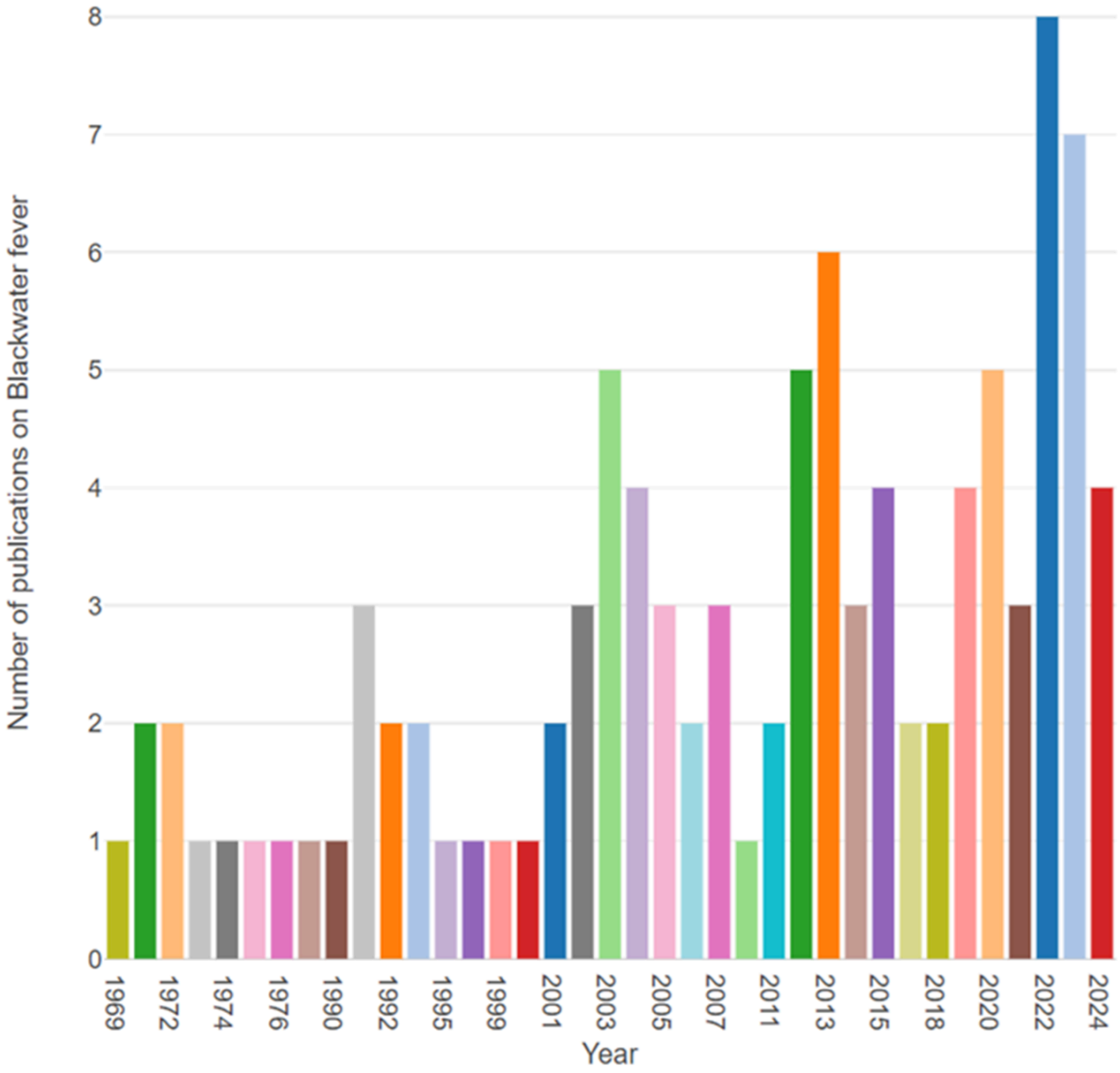

Figure 3

Geographical distribution of blackwater fever cases among children in Sub Saharan Africa

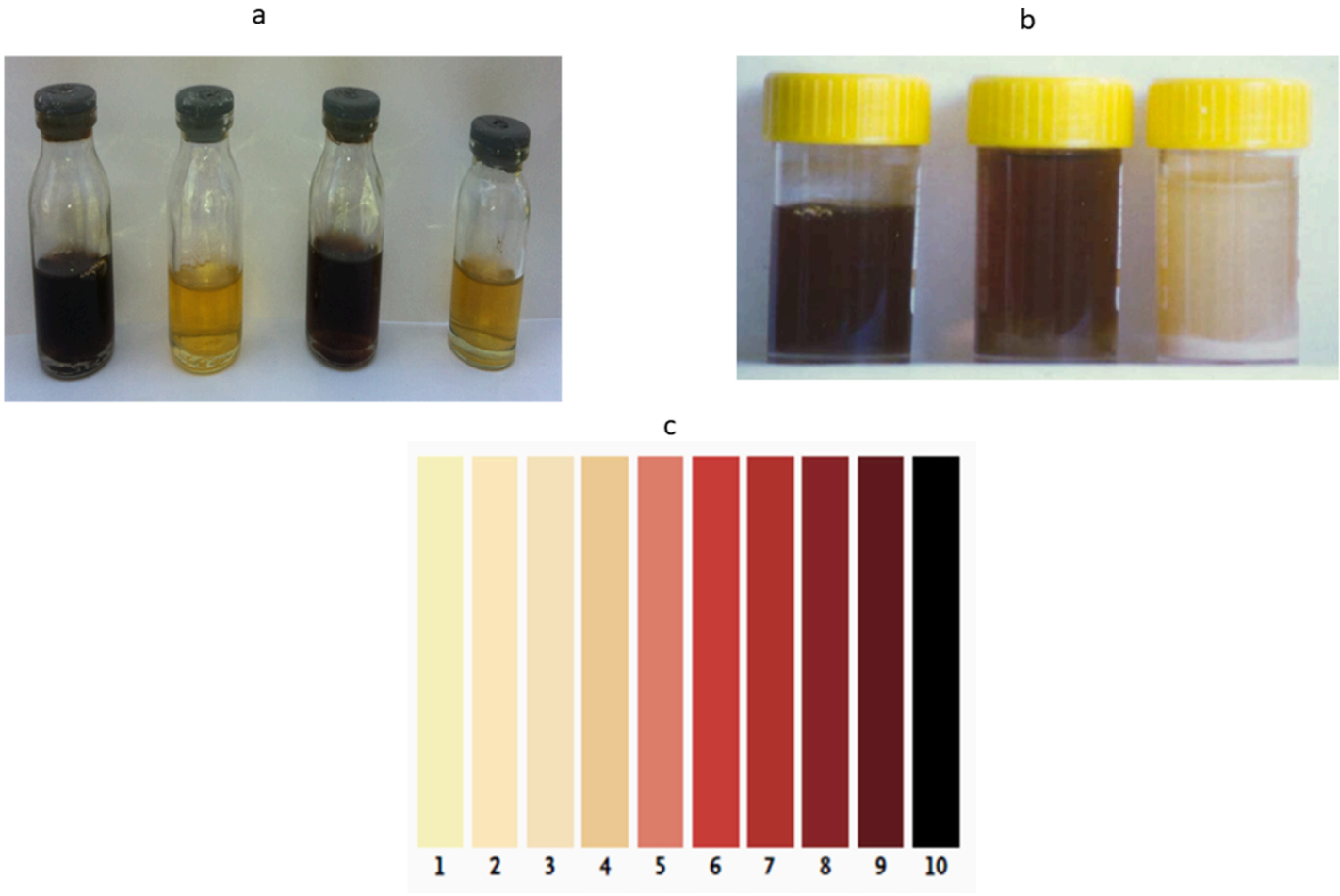

Figure 4

Figure 3. Use of the Hillmen urine colour chart to diagnose BWF. At admission, the patient/guardian was first asked to recall and match the colour of urine passed by their child on the day of admission to a colour on the HUCC. If available, urine was collected from the child using paediatric urine collection bags before it was transferred into the urine collection bottle. Then the attending study clinician then matched the urine colour to the corresponding score on the HUCC scale. Children with clinician- witnessed urine or patient/guardian matched colour of urine corresponding to HUCC >5 on the chart were confirmed to have BWF.

Supplementary Files

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

- Supplementary1PRISMAScRChecklist.pdf
- Supplementary2searchstrategy.pdf
- Supplementary3tableofincludedstudies.pdf
- Supplementary4Listofexcludedstudieswithreason.csv.csv