Summary of findings table for included studies on Blackwater fever in children in Sub-Saharan Africa (26 Studies)

No	Author (year)	Region/Country	Sample size	BWF cases (n/N %)	Study population characteristics	Objective	Main finding (s)
1	Gbadoé et al. (2006) [1]	Togo	361	62/361 (17.2%)	Hospitalized children aged 0–15 years with severe malaria at CHU-Tokoin, Lomé, during 2000–2002.	To describe the management, clinical evolution, and spectrum of severe pediatric malaria including BWF cases over a three-year period.	BWF prevalence increased to 17.2% by 2002; renal failure was present in 3% of cases; overall case fatality rate was 9.7%. Urgent transfusion and anti-malarial management were emphasized.
2	Ekvall et al. (2001) [2]	Tanzania	20	14/20 (70%)	Children aged 6 months to 4 years with parasitemia >1% in a malaria-endemic district.	To assess the type and extent of hemolysis (intravascular vs. extravascular) in falciparum malaria.	70% of children exhibited hemoglobinuria. Most hemolysis was extravascular based on biochemical markers, with only a minor intravascular component. Suggests BWF may often be misclassified.
3	Aloni et al. (2012) [3]	DR Congo	56	24/56 (42.8%)	Children under 13 years hospitalized with acute renal failure (ARF) at a tertiary pediatric hospital in Kinshasa between 2006 and 2009.	To evaluate clinical features, causes, and outcomes of ARF in children, focusing on BWF.	BWF was the most frequent cause of ARF (42.8%). Mortality was 25%. Dialysis access was very limited. BWF-associated ARF had high lethality and required improved diagnostic and therapeutic capacity.

4	Gobbi et al. (2005) [4]	Burundi	1039	9/1039 (0.9%)	Children <14 years with malaria at Kiremba Hospital.	To describe the clinical features, treatment, and outcomes of children diagnosed with blackwater fever in a malaria-endemic setting.	Nine cases of BWF were identified; all had recent quinine treatment. Treatment included transfusion and artemether. No deaths occurred. Authors suggest artemisinin as a safer alternative in such settings.
5	Namazzi et al. (2022) [5]	Uganda	598	Not directly reported (BWF analyzed as a predictor variable)	Children under 5 years of age hospitalized with severe malaria across two referral hospitals in Uganda as part of a prospective cohort study (2014–2017).	To determine the incidence of acute kidney injury (AKI), its progression to persistent kidney disease, and the role of BWF as a risk factor for poor post-discharge outcomes.	AKI was diagnosed in 45.3% of children. BWF was independently associated with both AKI and persistent kidney dysfunction. Children with BWF had significantly higher post-discharge mortality rates.
6	Daubrey et al. (2004) [6]	Côte d'Ivoire	41	41/41 (100%)	Children hospitalized in Abidjan with falciparum malaria who developed blackwater fever during or shortly after antimalarial treatment with quinine or amodiaquine	To describe the clinical features, timing, and outcomes of BWF cases that occurred during or after antimalarial therapy.	All 41 cases were triggered by quinine (88%) or amodiaquine (12%) use. Hemoglobinuria developed during the acute phase of malaria or early convalescence. 43% of children required transfusion; all recovered with supportive care.

7	Bodi et al. (2014) [7]	DR Congo	63	39/63 (61.9%)	Children aged 1 to 15 years hospitalized with acute renal failure (ARF) at the University Hospital of Kinshasa between 2009 and 2011.	To describe the etiology, clinical profile, and outcomes of ARF in children, particularly focusing on cases caused by blackwater fever	BWF was the leading cause of ARF, accounting for 61.9% of cases. 20 children required dialysis, but only a few could access it. The overall mortality rate was 22.2%, with BWF significantly associated with worse outcomes.
8	Bodi et al. (2013) [8]	DR Congo	129	43/129 (33.3%)	Children aged 2–15 years with confirmed blackwater fever (n=43) and controls with uncomplicated malaria (n=86) from four major pediatric facilities in Kinshasa.	To characterize the clinical presentation, laboratory abnormalities, and risk factors associated with BWF in Congolese children.	BWF cases had significantly higher rates of renal impairment, jaundice, and dark urine. Most BWF cases occurred during the rainy season. Quinine was used in 93% of BWF patients, and a significant number developed acute renal failure.
9	Opoka et al. (2020) [9]	Uganda	279	92/279 (33%)	Children under 5 years of age hospitalized with severe anemia at Jinja Regional Referral Hospital, and followed for 6 months post-discharge.	To determine post-discharge outcomes among children with SA and BWF.	BWF was associated with significantly higher 6-month risks of hospital readmission (HR = 1.68) and post-discharge mortality (HR = 3.37). Malaria was the leading cause of both initial and recurrent admissions.

10	Olupot-Olupot et al. (2017) [10]	Uganda	3170	394/3170 (12.4%)	Children aged 2 months to 12 years with severe febrile illness admitted to six hospitals in Eastern and Central Uganda (part of the FEAST trial, 2009–2011).	To assess BWF prevalence and outcomes among children with severe febrile illness.	BWF was identified in 12.4% of cases, especially in Eastern Uganda. Among BWF cases, 88.7% received transfusions. The condition was associated with severe anemia, jaundice, and increased hospitalization duration.
11	Ajetunmobi et al. (2012) [11]	Nigeria	251	48/251 (19.1%)	Children under 12 years admitted with severe malaria to the Emergency Pediatric Unit at University College Hospital, Ibadan.	To determine the incidence, risk factors, and complications associated with hemoglobinuria (BWF) in children with severe malaria.	Hemoglobinuria occurred in 19.1% of children. It was significantly associated with jaundice but not with G6PD deficiency. Renal failure occurred in 6.3% of hemoglobinuria cases. Routine urinalysis was recommended in severe malaria.
12	Namayanja et al. (2023) [12]	Uganda	300	158/300 (52.7%)	Children aged 2 months to 12 years admitted with severe malaria during a documented malaria epidemic at Mbale Regional Referral Hospital in 2021.	To describe the clinical spectrum and complications of severe malaria during epidemic period.	BWF was present in over half of severe malaria cases (52.7%). Jaundice and severe anemia were also common. Mortality rate was 6.3%. Metabolic acidosis and thrombocytopenia were predictors of

							prolonged hospital stay.
13	Paasi et al. (2021) [13]	Uganda (Eastern)	920	920/920 (100%)	Children under 15 years admitted with confirmed blackwater fever to Mbale and Soroti Regional Referral Hospitals from 2019 to 2021.	To identify predictors of mortality and prolonged hospitalization in BWF.	Mortality rate was 3.2%, with the majority of deaths occurring within 48 hours of admission. Independent predictors of death included altered consciousness, pallor, convulsions, and metabolic acidosis. Median hospital stay was 5 days.
14	Conroy et al. (2022) [14]	Uganda	999	82/999 (8.2%)	Children aged 6 months to 12 years hospitalized with acute febrile illness at Jinja Regional Referral Hospital in Eastern Uganda (2017–2019).	To investigate the relationship between blackwater fever (BWF) and acute kidney injury (AKI), and assess whether BWF independently contributes to in-hospital mortality.	BWF was independently associated with a 2.18-fold increased risk of AKI. However, AKI not BWF was the primary predictor of in-hospital mortality. BWF was also linked to endothelial activation and hemolysis.
15	Namazzi et al. (2024) [15]	Uganda	557	Not directly reported (BWF was a primary outcome variable)	Children aged 6 months to 4 years hospitalized with severe malaria at Mulago and Jinja hospitals and followed prospectively over	To evaluate the predictive role of circulating immune complexes (cIC) and glucose-6-phosphate dehydrogenase (G6PD) deficiency in recurrent	Elevated cIC levels strongly predicted BWF recurrence (aIRR 7.66). G6PD-deficient boys had higher cIC levels and were more likely to experience repeated BWF episodes.

					a 12-month post-discharge period.	blackwater fever episodes.	Mediation analysis supported an indirect role of G6PD deficiency through immune complex formation.
16	Connon et al. (2021) [16]	Uganda, Malawi	3894	165/3894 (4.2%)	Children aged 2 months to 12 years enrolled in the TRACT trial for severe anemia and followed post-discharge for up to 6 months	To determine the incidence and predictors of hospital readmission after discharge among children with severe anemia in malaria-endemic settings.	BWF accounted for 165 (4.2%) of all readmissions. Alongside HIV infection, missed medication doses, and prior transfusion, BWF was among the top three causes of readmission. Highlights the need for post-discharge monitoring in BWF cases.
17	Mzumara et al. (2021) [17]	Multi-Africa	5425	Not reported (BWF analyzed as a clinical predictor variable)	Children under 15 years with severe falciparum malaria enrolled in the AQUAMAT trial across 9 African countries between 2007 and 2010.	To identify prognostic indicators of metabolic acidosis and uraemia in severe malaria.	BWF was independently associated with increased odds of uraemia (adjusted OR = 1.58). Other strong predictors included coma, jaundice, shock, and hypoglycemia. Prompt recognition of BWF may aid in renal injury prevention.
18	Kunuanunua et al. (2015) [18]	DR Congo	378	96/378 (25.4%)	Children ≤13 years admitted with severe malaria to a	To describe the clinical presentations and	BWF remained frequent even after the shift from quinine to

					tertiary pediatric hospital in Kinshasa between 2012 and 2013, during the transition from quinine to artesunate.	complications of severe malaria, including blackwater fever, following the antimalarial treatment policy change.	artesunate, comprising over a quarter of severe malaria cases. It was strongly associated with severe anemia and metabolic acidosis. Case fatality rate was 4%.
19	Asio et al. (2022) [19]	Uganda	4913	4913/4913 (100%)	Surveillance data of BWF cases among children <12 yrs (2019–2021).	To describe BWF outbreak distribution and outcomes.	4913 cases were reported over 2 years; 26 deaths occurred (CFR 0.5%). Most children had malaria-positive rapid diagnostic tests. Relapses occurred every 2–3 weeks. Etiology of recurrent BWF remained unclear.
20	Opoka et al. (2020) [20]	Uganda	284	93/284 (32.7%)	Children aged 6 months to 5 years admitted with severe anemia to Jinja Regional Referral Hospital, many of whom had malaria and/or BWF.	To investigate inflammatory markers and immune mechanisms associated with severe anemia in children and assess whether BWF contributes to a heightened inflammatory response.	BWF was common among children with severe anemia and was associated with elevated systemic inflammatory markers (e.g., CRP, TNF-α). Malaria was nearly universal. Findings support a syndemic model of BWF, anemia, and malaria.
21	Bodi et al. (2020) [21]	DR Congo	129	43/129 (33.3%)	Children aged 2–15 years from 4 hospitals in	To investigate the association between MBL2 gene	Genotype AA was significantly more common in BWF

					Kinshasa. Cases had confirmed BWF, while controls had uncomplicated malaria.	polymorphisms and the occurrence of clinical BWF in Congolese children.	(72%) than in controls (50%). A0 genotype was protective (OR=0.21, p=0.019). Study suggests BWF may result from excessive immune activation, not MBL deficiency.
22	Bodi et al. (2018) [22]	DR Congo	90	30/90 (33.3%)	Children aged 2–15 years with either confirmed blackwater fever or uncomplicated malaria, matched by age and gender, from four hospitals in Kinshasa.	To evaluate malaria-specific IgG1 antibody levels in children with and without BWF.	IgG1 levels significantly higher in BWF cases; 95.3% received quinine; suggests immune-mediated hemolysis.
23	Eregu et al. (2023) [23]	Uganda (Eastern Region)	377	176/377 (46.7%)	Children aged 2 months to 12 years with WHO-defined severe malaria, admitted to Mbale Regional Referral Hospital during a seasonal malaria epidemic in 2023.	To quantify parasite density across the clinical spectrum of severe malaria and determine associations between parasite load and mortality or severe complications such as BWF.	BWF (haemoglobinuria) was the fourth most common severe malaria phenotype (46.7%). Mean parasite density was low (136,000/µL), with BWF cases having even lower densities (~98,000/µL). No significant association was found between parasite density and mortality. Study challenges the assumption that high

							parasitemia predicts severe malaria.
24	Paasi et al. (2021) [24]	Uganda (Eastern Region)	9578 pediatric admissions (1241 BWF cases)	1241/9578 (13.0%)	Children aged 2 months to 15 years admitted to Mbale and Soroti Regional Referral Hospitals between January and December 2018 with a clinical diagnosis of blackwater fever.	To describe the clinical characteristics, diagnostic practices, and treatment approaches for pediatric blackwater fever in two regional hospitals in Eastern Uganda.	BWF accounted for 13% of all pediatric admissions. It was more frequent in children older than 5 years. The most common clinical features were fever, pallor, jaundice, abdominal pain, and vomiting. There were no standardized diagnostic or treatment guidelines. Most children received antimalarials and blood transfusions.
25	Olupot-Olupot et al. (2020) [25]	Uganda (Eastern Region)	662	93/662 (14.0%)	Children aged 2 months to 12 years admitted to Mbale Regional Referral Hospital with WHO-defined severe malaria during a malaria epidemic in Eastern Uganda.	To describe the full clinical spectrum of severe malaria in children during an epidemic, including the burden and manifestations of blackwater fever.	BWF occurred in 14% of cases and was strongly associated with jaundice and severe anemia. Overall mortality was 9.5%. Common complications included respiratory distress and metabolic acidosis.
26	Dondorp et al. (2010) [26]	Multi-country (Uganda, Tanzania, Kenya, Nigeria, Ghana, Mozambique, Rwanda, The Gambia, DR Congo)	5425 children (<15 years)	116 (quinine group), 121 (artesunate group) – approx. 4.4% combined	Hospitalized children under 15 years with WHO-defined severe *Plasmodium falciparum* malaria enrolled in 11 sites	To compare the efficacy and safety of parenteral artesunate versus quinine in reducing mortality and complications in	Artesunate significantly reduced mortality (8.5%) compared to quinine (10.9%) — a 22.5% relative risk reduction. The trial also

					across sub-Saharan Africa.	African children with severe falciparum malaria.	observed fewer complications with artesunate, including coma progression and convulsions. While BWF was not the primary focus, it occurred in 4.4% of participants, and artesunate had slightly fewer BWF cases than quinine. The study led to WHO's recommendation of artesunate as first-line treatment for severe malaria in children.

1. Gbadoé, A.D., et al., *Évolution du paludisme grave de l'enfant au Togo de 2000 à 2002.* Médecine et Maladies Infectieuses, 2006. **36**(1): p. 52-54.
2. Ekvall, H., et al., *Acute haemolysis in childhood falciparum malaria.* Trans R Soc Trop Med Hyg, 2001. **95**(6): p. 611-7.
3. Aloni, M.N., et al., *Acute renal failure in Congolese children: a tertiary institution experience.* Acta Paediatr, 2012. **101**(11): p. e514-8.
4. Gobbi, F., et al., *Blackwater fever in children, Burundi.* Emerg Infect Dis, 2005. **11**(7): p. 1118-20.
5. Namazzi, R., et al., *Acute kidney injury, persistent kidney disease, and post-discharge morbidity and mortality in severe malaria in children: A prospective cohort study.* EClinicalMedicine, 2022. **44**: p. 101292.
6. Daubrey, T., et al., *Blackwater fever during antimalarial treatment in Abidjan (West Africa): 41 Cases report.* Bulletin de la Société de pathologie exotique (1990), 2004. **97**: p. 325-8.
7. Bodi, J.M., et al., *Black water fever associated with acute renal failure among Congolese children in Kinshasa.* Saudi J Kidney Dis Transpl, 2014. **25**(6): p. 1352-8.
8. Bodi, J.M., et al., *Blackwater fever in Congolese children: a report of clinical, laboratory features and risk factors.* Malar J, 2013. **12**: p. 205.
9. Opoka, R.O., et al., *Blackwater Fever in Ugandan Children With Severe Anemia is Associated With Poor Postdischarge Outcomes: A Prospective Cohort Study.* Clin Infect Dis, 2020. **70**(11): p. 2247-2254.
10. Olupot-Olupot, P., et al., *High Frequency of Blackwater Fever Among Children Presenting to Hospital With Severe Febrile Illnesses in Eastern Uganda.* Clin Infect Dis, 2017. **64**(7): p. 939-946.
11. Ajetunmobi, W.A., et al., *Haemoglobinuria among children with severe malaria attending tertiary care in Ibadan, Nigeria.* Malar J, 2012. **11**: p. 336.

12. Namayanja, C., et al., *Unusual clinical spectra of childhood severe malaria during malaria epidemic in eastern Uganda: a prospective study.* Malar J, 2023. **22**(1): p. 169.
13. Paasi, G., et al., *Predictors of prolonged hospitalisation and mortality among children admitted with blackwater fever in eastern Uganda.* Tropical Doctor, 2021. **52**: p. 004947552110467.
14. Conroy, A.L., et al., *Blackwater fever and acute kidney injury in children hospitalized with an acute febrile illness: pathophysiology and prognostic significance.* BMC Med, 2022. **20**(1): p. 221.
15. Namazzi, R., et al., *Circulating immune complexes and G6PD deficiency predict readmissions for blackwater fever and severe anemia in children with severe malaria in Eastern Uganda.* J Infect Dis, 2024.
16. Connon, R., et al., *Incidence and predictors of hospital readmission in children presenting with severe anaemia in Uganda and Malawi: a secondary analysis of TRACT trial data.* BMC Public Health, 2021. **21**(1): p. 1480.
17. Mzumara, G., et al., *Identifying prognostic factors of severe metabolic acidosis and uraemia in African children with severe falciparum malaria: a secondary analysis of a randomized trial.* Malar J, 2021. **20**(1): p. 282.
18. Kunuanunua, T.S., et al., *Severe malaria in children: A descriptive report from Kinshasa, the Democratic Republic of Congo.* J Trop Pediatr, 2015. **61**(4): p. 272-8.
19. Asio, A., et al., *Black Water Fever among children in Districts of Bugisu, Bukedi, and Busoga Region, Eastern Uganda, January 2019–July 2021.*
20. Opoka, R.O., et al., *Severe Anemia Is Associated with Systemic Inflammation in Young Children Presenting to a Tertiary Hospital in Uganda.* Am J Trop Med Hyg, 2020. **103**(6): p. 2574-2580.
21. Bodi, J.M., et al., *Exploring association between MBL2 gene polymorphisms and the occurrence of clinical blackwater fever through a case-control study in Congolese children.* Malar J, 2020. **19**(1): p. 25.
22. Bodi, J.M., et al., *High IgG1 malaria antibodies level in children is a possible risk factor of blackwater fever: a case-control study.* Pediatrics & Health Research, 2018. **3**(9).
23. Egiru, E.I.E., et al., *Low Malaria Parasite Density is Associated with Severe Malaria in Children in Eastern Uganda: a cross sectional study.* 2023.
24. Paasi, G., et al., *Characterising Childhood Blackwater Fever and Its Clinical Care at Two Tertiary Hospitals in Eastern Uganda.*
25. Olupot-Olupot, P., et al., *The clinical spectrum of severe childhood malaria in Eastern Uganda.* Malaria Journal, 2020. **19**: p. 1-9.
26. Dondorp, A.M., et al., *Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial.* The Lancet, 2010. **376**(9753): p. 1647-1657.