The aetiologies, mortality, and disability of non-traumatic coma in African children: a systematic review and meta-analysis

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Summary

Background Non-traumatic coma in African children is a common life-threatening presentation often leading to hospital attendance. We aimed to estimate the distribution of non-traumatic coma causes and outcomes, including disease-specific outcomes, for which evidence is scarce.

Methods We systematically reviewed MEDLINE, Embase, and Scopus databases from inception to Feb 6, 2024. We included studies recruiting children (aged 1 month to 16 years) with non-traumatic coma (Blantyre Coma Scale score ≤2, ie deep coma or comparable alternative) from any African country. Disease-specific studies were included if outcomes were reported. Primary data were requested where required. We used a DerSimonian–Laird random effects model to calculate pooled estimates for prevalence of causes, mortality, and morbidity (in-hospital and post-discharge), including analysis of mortality by temporality. This study was registered with PROSPERO (CRD4202014193).

Findings We screened 16 666 articles. 138 studies were eligible for analysis, reporting causes, outcome data, or both from 35 027 children with non-traumatic coma in 30 African countries. 114 (89%) of 128 studies were determined to be high quality. Among the causes, cerebral malaria had highest pooled prevalence at 58% (95% CI 48–69), encephalopathy of unknown cause was associated with 23% (9–36) of cases, and acute bacterial meningitis was the cause of 10% (8–12) of cases, with all other causes representing lower proportions of cases. Pooled overall case-fatality rates were 17% (16–19) for cerebral malaria, 37% (20–55) for unknown encephalopathy, and 45% (34–55) for acute bacterial meningitis. By meta-regression, there was no significant difference in cerebral malaria (p=0·98), acute bacterial meningitis (p=0·99), or all-cause coma (p=0·081) mortality by year of study. There was no substantial difference in deaths associated with cerebral malaria in-hospital compared with post-discharge (17% [16–19] *vs* (18% [16–20]). Mortality was higher post-discharge than in-hospital in most non-malarial comas, including acute bacterial meningitis (39% [26–52]) *vs* 53% [38–69]). Disability associated with cerebral malaria was 11% (9–12). Pooled disability outcomes associated with other non-malarial diseases were largely absent.

Interpretation The prevalence and outcomes of cerebral malaria and meningitis associated with non-traumatic coma were strikingly static across five decades. Enhanced molecular and radiological diagnostics, investment, policy making, community awareness, and health service provision are all required to facilitate earlier referral to specialist centres, to drive a step-change in diagnostic yield and treatment options to improve these outcomes.

Funding Wellcome Trust.

Lancet Glob Health 2025; 13: e1043–56

Published Online April 22, 2025 https://doi.org/10.1016/S2214-109X(25)00055-5

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For the Chichewa translation of the abstract see Online for appendix 1

For the French translation of the abstract see Online for appendix 2

For the Portuguese translation of the abstract see Online for appendix 3

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Introduction

Children in non-traumatic coma, defined as a Blantyre Coma Scale (BCS) score of two or less (on a scale of one to five, with a lower score indicating a deeper level of coma), frequently present to and die in hospitals across sub-Saharan Africa. In malaria-endemic regions, most cases of coma are attributed to cerebral malaria (unrousable coma with *Plasmodium falciparum* parasitaemia and no other identifiable cause). Non-infectious causes include metabolic abnormalities and toxins.[1–3] Limited availability of molecular and neuroimaging diagnostic resources in low-income settings and the high risk of asymptomatic malaria parasitaemia in malaria-endemic settings predispose the misclassification of cerebral malaria as the cause of non-traumatic coma, and they render alternative non-malarial diagnoses underdescribed (eg, acute bacterial meningitis).[4] A 5-year Kenyan study identified

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Research in context

Evidence before this study

Non-traumatic coma is a common hospital presentation in African children, and it is associated with poor outcomes compared with high-income settings. Causes include cerebral malaria, acute bacterial meningitis, viral encephalitis, and metabolic or toxin derangement. Poor availability of molecular and radiological diagnostic resources, alongside overlapping clinical features, challenge accurate causal classifications in non-traumatic coma studies. Similarly, estimates of long-term mortality and disability outcomes are scarce. On searching the literature, we identified one systematic review of the causes of non-traumatic coma in African and Asian children, but this did not include any outcome estimates or a meta-analysis to estimate the prevalence of causes. One meta-analysis described that the mortality rate from severe malaria in Melanesian children is lower than in Africa and Asia. We are unaware of any systematic review and meta-analysis to have assessed the causal distributions, mortality, and morbidity of non-traumatic coma in African children.

Added value of this study

To our knowledge, this is the first systematic review and meta-analysis examining the causal distributions, mortality, and disability of non-traumatic coma in African children. We included 138 studies, from database inception up to Feb 6, 2024, from 30 African (predominately sub-Saharan) countries, spanning over 50 years. Most studies were determined as high quality. In addition, ten key studies agreed to data-sharing agreements to enhance disease estimates. Cerebral malaria was consistently the most common cause of non-traumatic coma. The relative proportion of cerebral malaria causing non-traumatic coma remained essentially static across the entire study period, despite the known reduction in malaria incidence over that time. The next most common cause was coma of unknown aetiology. This finding probably reflects limitations in diagnostic capacity. Bacterial meningitis was the most common non-malarial coma presentation. There were few data on cerebral malaria and bacterial co-infection. Overall, mortality rates were unacceptably high, with death reported in almost one third of children. Strikingly, case-fatality rates were essentially static for cerebral malaria and bacterial meningitis over the entire study period. Bacterial meningitis resulted in the highest case-fatality rate: it was fatal in half of the children. Disability was found in one in ten children surviving cerebral malaria. However, this finding on disability prevalence is likely to be an underestimate due to a scarcity of long-term neurocognitive estimates. There were few estimates on the prevalence of non-malarial coma-related disability.

Implications of all the available evidence

Our analysis highlights the consistently high rate of children in coma who continue to die from malaria and meningitis in Africa despite the overall reduction in incidence and mortality from these diseases through malaria control and vaccine programmes. Our study emphasises the need for future large, high-quality, prospective longitudinal studies to apply rigorous diagnostics and neurodevelopmental assessments to improve knowledge on pathogenic cause and long-term outcome in non-traumatic coma among African children (see paired cohort study). Moreover, a step-change is needed to improve the unacceptably poor and static outcomes for non-traumatic coma. Enhanced investment, policy making, community awareness, and health service provision are all required to facilitate earlier referral to specialist centres and optimised treatment. Further investigation of both underlying pathobiological mechanisms of coma and affordable pragmatic neuroprotective supportive therapies are needed to make inroads to reducing mortality.

decreasing proportions of cerebral malaria alongside a reciprocal increase in comas with unknown cause in over half of children with non-traumatic coma,[4] and similar trends were observed in Malawi between 2006 and 2023 (unpublished). Differentiating bacterial infection with coma from cerebral malaria is challenging, and they probably frequently co-exist. Treatment for coma is therefore often empirical, and WHO recommends children with coma receive both parenteral antimalarials and antibiotics.[5] However, antibiotics are often withheld if a child has a positive malaria blood film or the lumbar puncture is delayed, with resultant probable undertreatment of bacterial infection, increasing risk of death.[5] A previous systematic review (14 studies from Africa and Asia) exists, but without single-disease studies or meta-analysis, necessitating a rigorous updated meta-analysis (to include recent enhanced diagnostic aetiology studies and disease-specific disability and mortality estimates) to guide clinicians working in malaria-endemic settings to provide optimal care.[6] We aimed to primarily evaluate the available evidence to evaluate the causes (infectious and non-infectious) of non-traumatic coma in African children, and the diagnostic approaches used to establish such causes. We also aimed to determine the mortality and morbidity (characterised as neurological disability) of all-cause and disease-specific states of non-traumatic coma in African children.

Methods

Search strategy and selection criteria

We performed a systematic review and meta-analysis of studies describing the cause and outcome of non-traumatic coma in African children. Ethical approval was not required. We included observational (cross-sectional, cohort, and case–control) and experimental (cluster and individually randomised controlled trials [RCTs], and quasi-experimental) studies recruiting children aged

between 1 month and 16 years with any coma from any African country. We included articles defining coma as BCS score of two or less (defined by WHO as deep coma in cerebral malaria) or a comparable alternative (eg, Glasgow Coma Scale ≤8). Using the WHO coma definition, which is the most frequently used definition within African studies, allows for review of a comparable level of coma in non-malarial causes and minimises heterogeneity. This definition is also more likely to capture CNS infections; for example, it will help to differentiate coma from severe febrile illness with a transient alteration in conscious level. Further analysis including studies of any level of altered consciousness is available in appendix 4 (pp 61–62).

Articles were included if it was possible to disaggregate the total number of children with non-traumatic coma and to extract the coma cause or outcome data. We then produced pooled estimates of proportions of causes by individual disease type. Given the heterogeneity of included cause types in individual studies, cumulative median pooled estimates of all disease prevalences do not equate precisely to 100%. Disease-specific studies were included providing coma was associated and outcomes reported. Individual study definitions of syndromes, for example meningitis, were accepted (appendix 4 p 3). Morbidity was defined as neurological sequelae or disability related to the illness (eg, cognitive, motor, visual and hearing impairment, and epilepsy). Case reports, case series, commentaries, and editorials were excluded, as were publications not containing primary data.

MEDLINE, Embase, and Scopus databases were searched with no date restrictions but limited to English and French articles. Search strings included Africa and the countries therein, and permutations of "coma", "aetiology", and "child" (appendix 4 p 3). Conference proceedings and databases of ongoing studies (including ClinicalTrials.gov, ISRCTN registry, and the WHO International Clinical Trials Registry Platform portal), along with reference lists of eligible studies and relevant reviews were searched to identify additional candidate studies. Grey literature was excluded. When required, attempts to contact study authors for primary data were made.

STJR and CEF independently assessed titles and abstracts. The full text of identified studies was individually assessed for eligibility against the predetermined criteria described above by two reviewers (two of STJR, CEF, and AB for each article), with disagreements resolved by consensus or third reviewer. Our review was conducted in accordance with PRISMA recommendations. The published protocol is available from https://rdcu.be/cZOUp (appendix 4 p 4).

Data analysis

The Cochrane standard data collection form was adapted for extraction (appendix 4 pp 4–11) and was piloted on a randomly selected subset of 10% of included studies, with a computation of the reviewers' reliability. Reviewers extracted data independently and then corroborated the data retrieval from each eligible study via an online form into spreadsheet format. Data on causes in all included studies, with both usual care and treatment arms for RCTs, were recorded as reported and were summarised using a DerSimonian-Laird random effects model meta-analysis. Heterogeneity was quantified with τ^2, I^2, and Cochran's Q test (H^2).[7] Duplicate data were excluded.

Subgroup analyses included meta-analysis of both coma (BCS ≤2 or comparable alternative), and any level of altered consciousness (BCS ≤4 or equivalent), in studies that reported disease-specific causes for both deep coma and any level of altered consciousness. In-hospital and post-discharge mortality are presented as simple proportions with exact binomial confidence intervals; pooled mortality estimates were calculated using a

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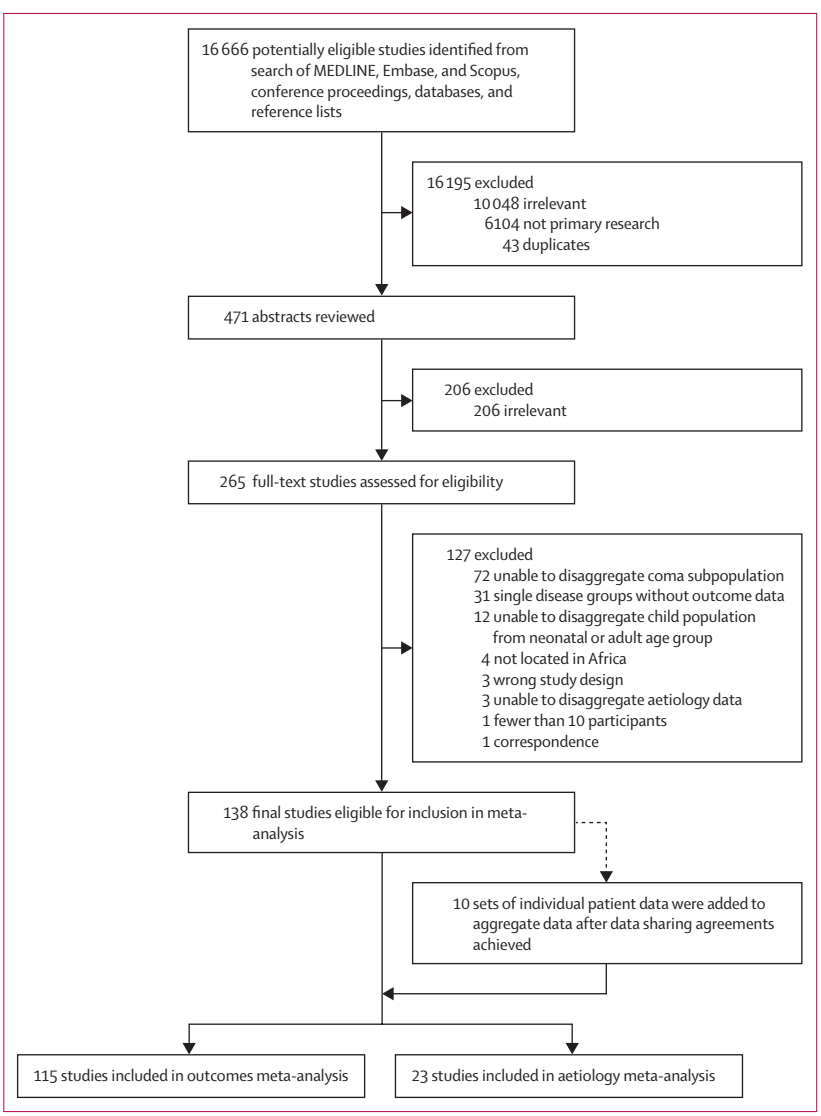

Figure 1: **Study selection flowchart**

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DerSimonian-Laird random effects model. Estimates included outcomes only in the standard care arm of RCTs, except cerebral malaria studies where a sensitivity analysis was performed including studies using artemisinin derivatives (eg, artesunate, given that this drug class is now standard of care as per WHO guidelines). Heterogeneity was explored by meta-regression. Covariates included year of recruitment, geographical region, gross domestic product per capita, median age, proportion of HIV infection, metabolic acidosis (evidenced by blood gas or cardinal respiratory features), seizure event, and secondary co-infection as fixed effects for all-cause and cerebral malaria mortality. We also tested for improved model fit by likelihood ratio testing of nested models. In all analyses, a p value of <0·05 was considered statistically significant.

Cerebral malaria mortality comparisons across multiple timepoints, a protocol deviation in response to initial findings, were undertaken at three timepoints: 2007, 2012, and 2015; these timepoints were chosen pragmatically to mirror Global Burden of Disease temporal estimates of deaths resulting from malaria.[8] We estimate oral artemisinin combination therapy replaced sulfadoxine-pyrimethamine across Africa in 2007,[9] distribution of insecticide-treated bednets around 2012,[10] and widespread use of rapid diagnostic testing and intravenous artesunate as first-line therapy by 2015.[11]

Bias assessments were performed independently by STJR, CEF, and AB, with disagreements resolved by consensus or a third reviewer. The validated Cochrane Risk of Bias tool (RoB 2.0)[12] and the modified Newcastle–Ottawa Scale (NOS)[13] quality assessment tool were used to formulate a bespoke modified NOS for all study types (appendix 4 pp 12–13). Overall quality was rated as high (ie, a low risk of bias across all domains), medium, or low.

Statistical analyses were performed with Stata (versions 15.1 and 18.5) and GraphPad Prism (version 9.0.0). This review is also registered on PROSPERO (CRD4202014193).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

16 666 articles were screened up to Feb 6, 2024. 138 studies were included, including 35 027 children (figure 1). Study publication spanned March, 1971–December, 2023 (appendix 4 pp 17–26). Email requests were sent to 11 authors, with data sharing agreed for ten studies (appendix 4 p 13).

Included studies were from 30 African countries: 65 from east Africa (47%),[1,4,14–69] 48 from west Africa (35%),[2,70–115] ten from north Africa (7%),[3,116–122] seven from central Africa (5%),[123–129] one from south Africa (1%),[130] and seven (5%) were multi-country studies (figure 2).[131–136] 21 studies took place in rural hospitals, and the remainder were from urban centres or mixed multi-centres. Kenya (n=7320 participants; data from 21 studies) and Malawi (n=9699; data from 19 studies) had the most studies. The high volume of studies from east and west Africa reflects the so-called meningitis belt (a geographical band across the middle of the African continent with a high risk of meningitis [particularly meningococcal meningitis] outbreaks). Consistent data have been published across the review study period from Kenya, Malawi, and Nigeria, with Uganda publishing after 2000. There is a paucity of published research from northern and southern Africa (figure 2).

We included 89 (64%) prospective observational cohorts, 26 (19%) retrospective cohorts, 19 (14%) RCTs, and four (3%) cross-sectional studies (appendix 4 pp 17–26). 23 (17%) studies were grouped non-traumatic coma studies that reported available clinical data, laboratory data, or both on multiple causes within the cohort. 115 (83%) studies were single-disease cohorts with available outcome data. Participant median age (reported in 51 [37%] studies) was 39·5 months (IQR 43·8–46·9). Definitions of coma were heterogenous between studies, although most (103 [75%]) used a validated tool (eg, BCS). 49 (36%) studies

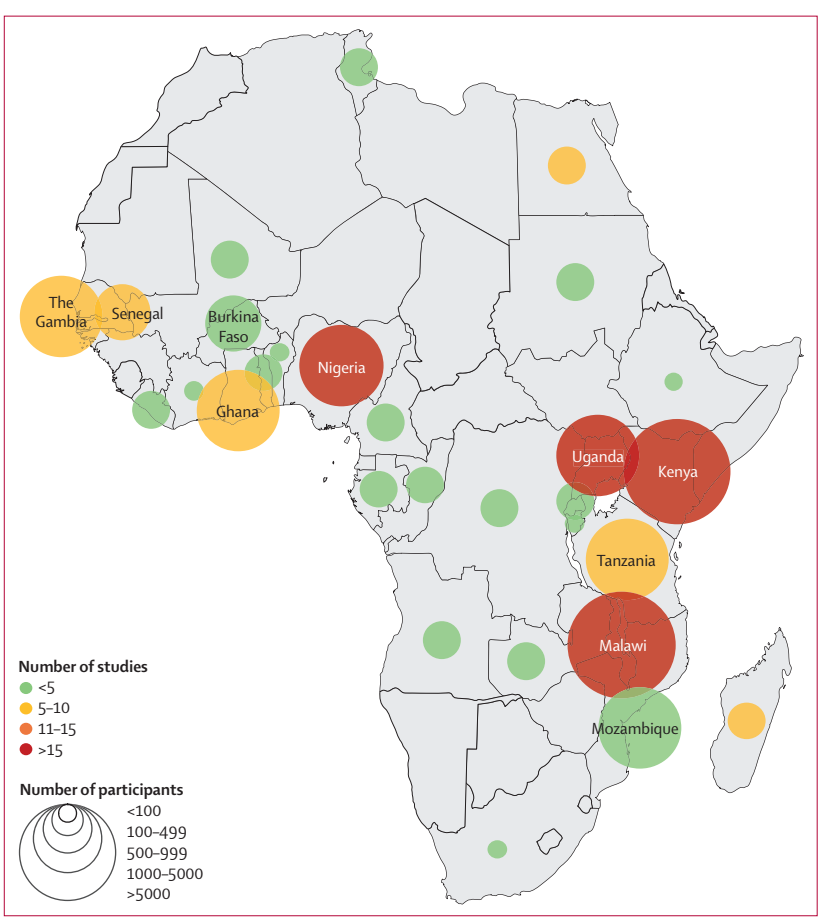


Figure 2: **Number of studies and participants per African country**

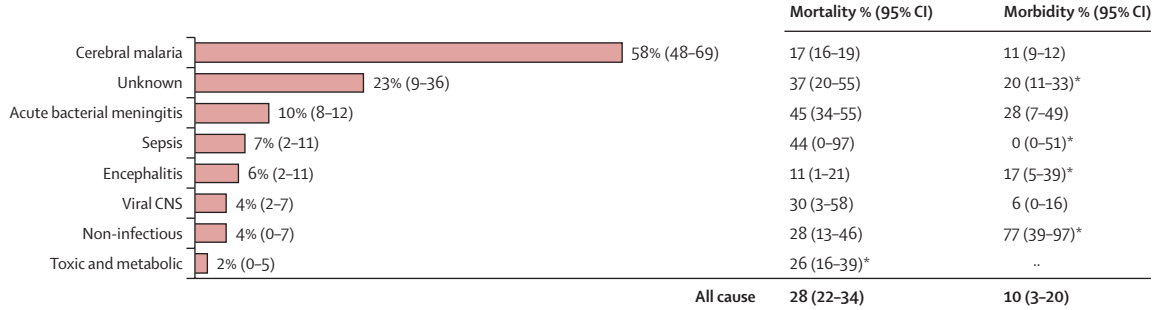
described children with any level of altered consciousness (including coma), and 89 (64%) included only children in a coma.

Pathogen data were available from 23 studies. All 23 (100%) reported results yielded from blood culture, cerebrospinal fluid microscopy, culture, and sensitivities, and malaria blood films, but only 12 (52%) reported individual results. Four (17%) of these studies additionally used malaria rapid diagnostic tests. Eight (35%) studies reported PCR diagnostic findings from stored cerebrospinal fluid. Four (17%) studies[1,19,136,137] targeted up to 14 viruses and one (4%) only targeted bacteria (specifically, bacterial meningitis).[124] Three (13%) studies targeted both viruses and bacteria.[20,138,139] One (4%) study used viral metagenomics.[139] Neuroimaging was reported in two (9%) studies; however, only one (4%),[3] conducted outside of sub-Saharan Africa, reported imaging results to support syndromic classification.

Cerebral malaria was consistently the most prevalent cause of non-traumatic coma, with a pooled prevalence of 58% (95% CI 48–69; data from nine studies). Encephalopathy of an unknown cause had a pooled prevalence of 23% (9–36; five studies), acute bacterial meningitis was 10% (8–12; ten studies), sepsis was 7% (2–11; six studies), encephalitis was 6% (2–11; four studies), and viral meningitis was 4% (2–7; two studies). Pooled prevalence was 2% (0–5; three studies) for toxic and metabolic causes and 4% (2–7; two studies) for non-infectious causes (figure 3, appendix 4 pp 32–37). Pathogen diagnosis was reported infrequently; the most common (pooled) isolated bacterium was *Streptococcus pneumoniae* in both cerebrospinal fluid (52 [40%] of 131 samples; five studies) and blood (13 [25%] of 53; four studies), followed by *Haemophilus influenzae* (18 [20%] of 93; four studies) in cerebrospinal fluid and *Staphylococcus aureus* in blood (14 [25%] of 64; four studies), then non-typhoidal *Salmonella* in both cerebrospinal fluid (7 [11%] of 61; two studies) and blood (5 [19%] of 27; two studies). These data reflect the proportions of patients with each pathogen that are reported in those with acute bacterial meningitis without coma. The pooled proportion of co-infection (viral, bacterial, or both) in cerebral malaria was estimated to be 15% (9–22; seven studies; appendix 4 p 31). The causal proportions stayed relatively constant over time, except encephalopathy of unknown cause, with lower proportions of unknowns due to implementation of molecular diagnostics yielding higher numbers of causative pathogens and therefore confirmed coma causes (data from three studies; appendix 4 pp 32–37).

Outcome data were available from 23 studies investigating multiple underlying causes of non-traumatic coma, but only three reported outcome data post-discharge (at 1 month, 6 months, and 3–12 months). The pooled estimate of coma mortality from these studies was 28% (95% CI 22–34; data from 18 studies; appendix 4 pp 38–40).

Outcome data for single diseases could be extracted from 115 studies. 102 studies reported mortality with or without additional morbidity data, and 13 reported morbidity data only (figure 3). The pooled estimate of mortality associated with cerebral malaria was 17% (95% CI 16–19; data from 85 studies; figure 4; appendix 4 pp 45–46), with no clear trend in mortality over time. This finding remained consistent across sensitivity analyses for only-control arms and only-artemisinin arms of RCTs (appendix 4 pp 41–44). Across Africa, mortality associated with cerebral malaria was not significantly different before and after 2007 (17% [data from 44 studies] *vs* 18% [37 studies], p=0·21), or before and after 2012 (18% [58 studies] *vs* 18% [23 studies], p=0·28; figure 4, appendix 4 p 45). There was a modest reduction in the case-fatality rate associated with cerebral malaria before versus after 2015 (19% [66 studies] *vs* 17% [15 studies], p=0·0038). However, the three timepoints show an absence of consistent improvement in cerebral malaria mortality over time, also illustrated by meta-regression (p=0·41; appendix 4 p 46). Within the three studies reporting co-infection, any co-infection with cerebral malaria was associated with higher mortality than the mortality for cerebral malaria alone (36% [20–52] *vs* 22% [8–36], p<0·0001; three studies; appendix 4 p 48). There was no significant difference in cerebral malaria mortality comparing in-hospital (17% [16–19]) versus post-discharge timepoints (18% [16–20]).



	Mortality % (95% CI)	Morbidity % (95% CI)
Cerebral malaria	17 (16–19)	11 (9–12)
Unknown	37 (20–55)	20 (11–33)*
Acute bacterial meningitis	45 (34–55)	28 (7–49)
Sepsis	44 (0–97)	0 (0–51)*
Encephalitis	11 (1–21)	17 (5–39)*
Viral CNS	30 (3–58)	6 (0–16)
Non-infectious	28 (13–46)	77 (39–97)*
Toxic and metabolic	26 (16–39)*	..
All cause	28 (22–34)	10 (3–20)

Figure 3: **Pooled prevalence, morbidity, and mortality of causes of non-traumatic coma**
*Single-study data.

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See **Online** for appendix 4

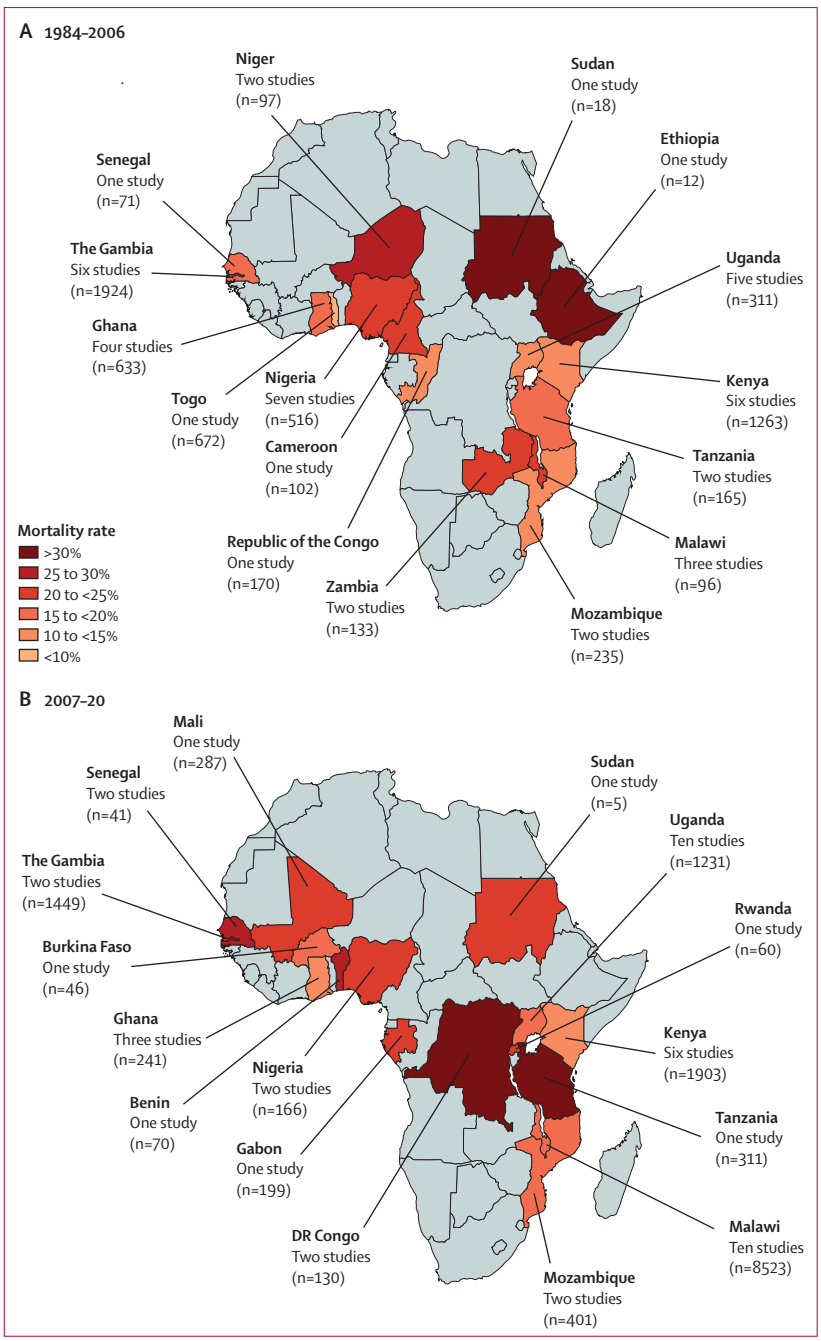


Figure 4: **Studies of cerebral malaria-related mortality per African country in 1984–2006 (A) and 2007–20 (B)**
Difference in pooled cerebral malaria-related mortality before and after 2007, p=0·215.

Conversely, mortality was higher post-discharge compared with in-hospital following most non-malarial comas, including those associated with acute bacterial meningitis (39% [26–52] *vs* 53% [38–69]; figure 5; appendix 4 p 51).

The pooled mortality estimate of coma associated with acute bacterial meningitis was 45% (95% CI 34–55; data from 16 studies; appendix 4 p 49). The case-fatality rate associated with encephalopathy of unknown cause was 37% (20–55; seven studies), with sepsis was 44% (0–97; four studies), with viral meningitis infection was 30% (3–58; three studies), with non-infectious causes was 28% (13–46; two studies), and with encephalitis was 11% (1–21; two studies). There were no pooled studies to perform mortality estimates of toxic and metabolic causes (appendix 4 pp 51–52).

In the three studies that investigated multiple causes of coma, the pooled estimate of disability was 10% (95% CI 3–20). The pooled disability estimate for cerebral malaria (when including artemisinin treatment arms of RCTs) was 11% (9–12; data from 39 studies), 28% for acute bacterial meningitis (7–49; three studies), and 6% for viral CNS infections (0–16; two studies). There were insufficient studies to perform pooled disability estimates for the remaining causes, but single studies report disability estimates of 20% for encephalopathy of unknown causes (11–33), 0% for sepsis (0–51), 17% for encephalitis (5–39), and 77% for non-infectious causes (39–97). There were no studies reporting disability outcomes in toxic or metabolic coma (appendix 4 p 52).

Heterogeneity was explored with meta-regression (appendix 4 pp 54–60). Positive HIV status (only seven studies with rigorous data) was associated with a significantly higher mortality (p=0·023) identified in the 23 studies investigating multiple non-traumatic causes, but not with mortality associated with coma caused by cerebral malaria (p=0·17). There was a significant association between African regions and deaths associated with cerebral malaria (with the highest case-fatality rates in north and west Africa [p=0·03; appendix 4 p 55]). A comparison of case-fatality rates in east Africa and west Africa (the two regions where most studies were published) also showed a significantly higher mortality in west Africa (p<0·0001; appendix 4 p 55). Deaths associated with grouped causes of non-traumatic coma overall were not increased in any region. No other variables were significantly associated with mortality due to coma of any cause or coma from cerebral malaria, although only six studies reported retinopathy status (therefore meaning that an absence of association could be due to underpowering rather than a true absence).

Using the modified NOS, 114 (89%) of 138 studies were determined to be high quality (score ≥6; appendix 4 pp 13–16). The most frequent risks of bias found in the included studies were poor ascertainment of exposure, absence of validated or any definition of coma, non-reproducible description of diagnostic testing, and failure to report follow-up rate.

Discussion

We systematically reviewed the causes and outcomes of African children with non-traumatic coma, analysing 138 studies (most of which were determined to be high quality) from 30 countries published across 53 years.

Cerebral malaria was the dominant cause of coma (58%), followed by an unknown cause (23%), and acute bacterial meningitis (10%). Outcomes were universally poor, with a 28% mortality rate associated with all-cause coma. Acute bacterial meningitis resulted in the highest proportion of deaths (45%), with cerebral malaria having the lowest proportion across the dominant causes (17%). There was no significant reduction in the case-fatality rate associated with cerebral malaria, acute bacterial meningitis, or all-cause coma since 1971. There was no difference in deaths associated with cerebral malarial comas in-hospital compared with post-discharge, yet mortality rate increased after discharge in patients with non-malarial coma. Disability was infrequently reported on after non-traumatic coma outside of those caused by cerebral malaria.

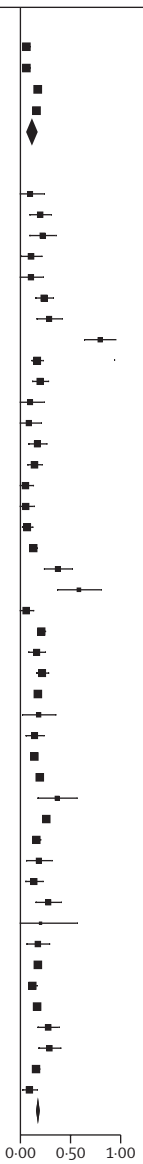
Strikingly, the proportion of children with non-traumatic coma attributable to cerebral malaria remained static across the study period, despite a significant reduction in malaria incidence in Africa following effective malaria control programmes.[10] Why the proportion of non-traumatic coma attributable to cerebral malaria has not fallen is unclear. With bed-net rollout, low malaria transmission might influence the acquisition of immunity and promote a higher relative incidence of more severe forms of malaria,[32] with more older children hospitalised with cerebral malaria due to lower immunity at a younger age;[140] however, not all studies have seen this trend.[141] The proportions of acute bacterial meningitis were also static over time despite widespread vaccination in the past three decades. Crucially, we cannot infer incidence and therefore overall burden of disease from our included studies. Viral encephalitis diagnosis was infrequently reported, probably due to low imaging and PCR diagnostic capacity.

For the first time—to our knowledge—our meta-analysis shows a substantial reduction in the proportion of non-traumatic coma with unknown causes over the past 2 years. These most recent studies, alongside our prospective cohort study on febrile coma in Malawi (see paired Article[142]), illustrate the enhanced diagnostic yield achieved by applying molecular diagnostics. There is a clear dearth of pathogen-driven causal classifications in our analysis, with only eight studies utilising molecular diagnostic tools (mostly against viral targets). We strongly encourage rapid scaling up and deployment of affordable molecular multiplex diagnostics across Africa to improve diagnosis and management of critical illness in African children. Access to molecular diagnostics in Africa has historically been low, but rapid global implementation of COVID-19 PCR testing amid the pandemic presents an obvious platform upon which to extend in-hospital molecular testing; the COVID-19 pandemic also illustrated the remarkable achievements that can occur when multinational policy, governments, charities, and industry synergise towards a common global priority. Similar cohesions will be required to disseminate equipment and facilitate the continued funding for maintenance and consumables for regular use. The WHO target product profile for low-cost testing in bacterial meningitis is a promising start,[143] yet there remains unlocked potential for further synergy across global organisations to widen equitable access to PCR diagnostics in Africa.

Similarly, neuroimaging in Africa to support both diagnosis and prognostication is underused. With 40 times more scanners and over 100 times more radiologists in high-income settings compared with Africa, scaling up equipment and radiological expertise

A

	Number of successes	Total	Proportion (95% CI)	Weight (%)
Unknown timepoint				
Carter et al (2005)	14	244	0·06 (0·03–0·09)	1·59%
Carter et al (2005)	14	244	0·06 (0·03–0·09)	1·59%
Mbale et al (2016)	214	1301	0·16 (0·14–0·18)	1·66%
Lin et al (2022)	182	1192	0·15 (0·13–0·17)	1·65%
Heterogeneity: τ^2=0·00, I^2=95·24%, H^2=21·02			0·11 (0·05–0·16)	..
Hospital discharge CFR				
Wolf-Gould et al (1992)	2	20	0·10 (0·00–0·23)	0·66%
Walker et al (1992)	11	56	0·20 (0·09–0·30)	0·85%
Gordeuk et al (1992)	9	41	0·22 (0·09–0·35)	0·69%
Taylor Q et al (1993)	4	37	0·11 (0·01–0·21)	0·89%
Taylor A et al (1993)	3	28	0·11 (0·00–0·22)	0·77%
Wright et al (1993)	22	94	0·23 (0·15–0·32)	1·02%
Krishna et al (1994)	15	53	0·28 (0·16–0·40)	0·72%
Waller et al (1995)	21	27	0·78 (0·62–0·93)	0·52%
Marsh et al (1995)	31	185	0·17 (0·11–0·22)	1·35%
English et al (1996)	20	102	0·20 (0·12–0·27)	1·11%
Akpede (1996)	2	20	0·10 (0·00–0·23)	0·66%
Newton et al (1997)	2	23	0·09 (0·00–0·20)	0·77%
Imbert et al (1997)	12	71	0·17 (0·08–0·26)	1·00%
Schellenberg et al (1999)	14	99	0·14 (0·07–0·21)	1·19%
Assimadi Q et al (2002)	2	37	0·05 (0·00–0·13)	1·15%
Assimadi QL et al (2002)	2	35	0·06 (0·00–0·13)	1·11%
Idro et al (2003)	7	100	0·07 (0·02–0·12)	1·39%
Maitland et al (2003)	52	400	0·13 (0·10–0·16)	1·56%
Mockenhaupt et al (2004)	18	49	0·37 (0·23–0·50)	0·64%
Gay-Andrieu et al (2005)	12	21	0·57 (0·36–0·78)	0·33%
Schubart et al (2006)	3	49	0·06 (0·00–0·13)	1·21%
Evans et al (2006)	100	481	0·21 (0·17–0·24)	1·53%
Namutangula et al (2007)	13	80	0·16 (0·08–0·24)	1·07%
Issifou et al (2007)	43	199	0·22 (0·16–0·27)	1·32%
Bronzan et al (2007)	211	1210	0·17 (0·15–0·20)	1·65%
Bassat et al (2008)	4	22	0·18 (0·02–0·34)	0·50%
Idro et al (2008)	9	63	0·14 (0·06–0·23)	1·01%
O'Meara et al (2008)	167	1194	0·14 (0·12–0·16)	1·66%
Helbok et al (2009)	415	2150	0·19 (0·18–0·21)	1·68%
Camara et al (2010)	9	25	0·36 (0·17–0·55)	0·40%
Jallow et al (2012)	286	1116	0·26 (0·23–0·28)	1·62%
Gwer et al (2012)	63	393	0·16 (0·12–0·20)	1·53%
Gwer et al (2013)	7	38	0·18 (0·06–0·31)	0·71%
Oluwayemi et al (2013)	9	66	0·14 (0·05–0·22)	1·05%
Mallewa et al (2013)	14	51	0·27 (0·15–0·40)	0·72%
El-Amin et al (2013)	1	5	0·20 (0·00–0·55)	0·14%
Maltha et al (2014)	8	46	0·17 (0·06–0·28)	0·81%
Moxon et al (2016)	396	2269	0·17 (0·16–0·19)	1·68%
Villaverde et al (2017)	31	254	0·12 (0·08–0·16)	1·49%
Borgstein et al (2022)	277	1663	0·17 (0·15–0·18)	1·67%
Namazzi et al (2022)	20	73	0·27 (0·17–0·38)	0·87%
Brisset et al (2022)	20	70	0·29 (0·18–0·39)	0·84%
MacCormick et al (2022)	86	549	0·16 (0·13–0·19)	1·58%
Edridge et al (2023)	6	65	0·09 (0·02–0·16)	1·17%
Heterogeneity: τ^2=0·00, I^2=81·89%, H^2=5·52			0·17 (0·16–0·19)	..



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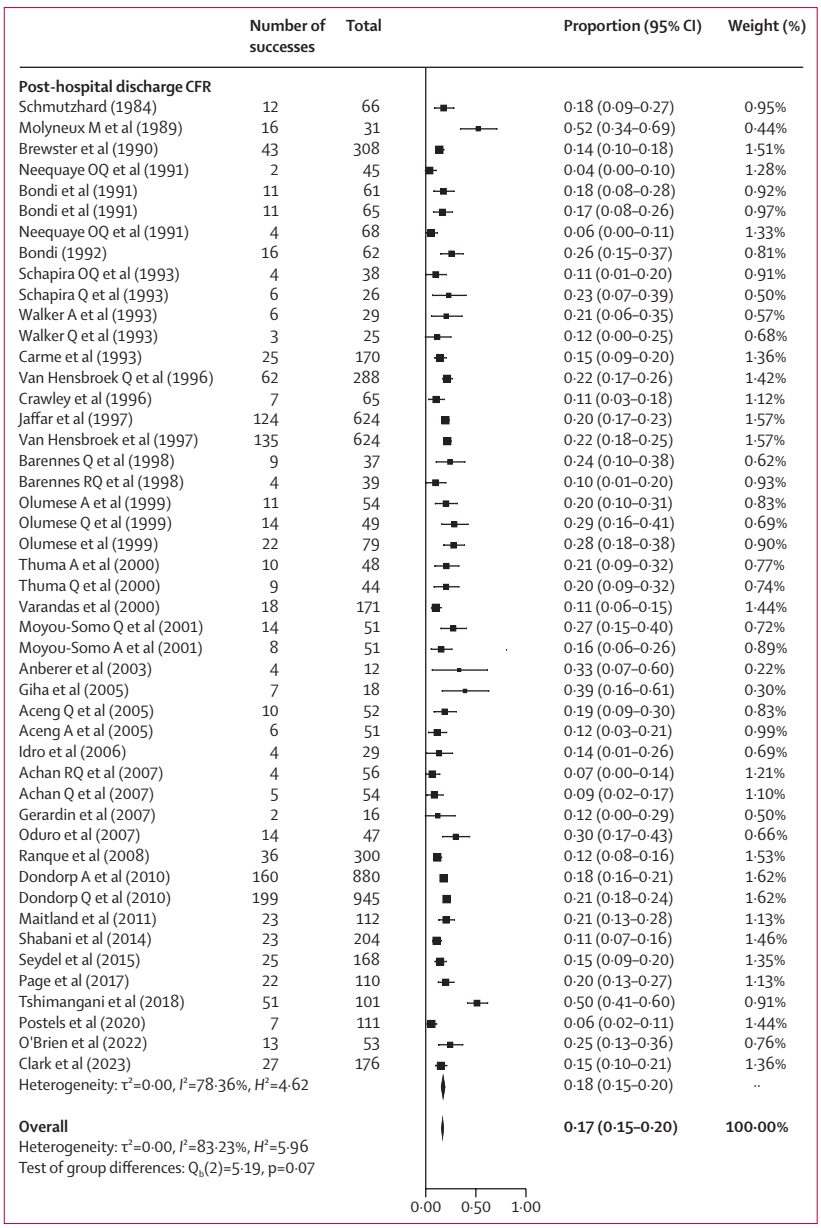

(Figure 5 continues on next page)

is challenging. Alternative approaches are being developed, including low-field, lower-cost portable MRI imaging with cloud-based remote reporting.[144]

Another striking finding was the consistently high mortality among children with non-traumatic coma over the past five decades. These high fatality rates associated with all-cause coma and cerebral malaria mirror the findings from a previous meta-analysis of severe malaria[145] and systematic review of non-traumatic coma.[6] Despite the Global Burden of Disease studies reporting substantial reduction in overall malaria mortality since 2017,[8] cerebral malaria mortality has remained essentially static with no consistent trend in improvement across the three timepoints (appendix 4 pp 45–46). Despite the variation in distribution, timing and effectiveness of malaria control interventions across the continent,[146] this observation remains discouraging. Such static outcomes could be predetermined by low care-seeking behaviour and difficulties with access to specialist centres, with resultant late presentation to specialist care.[147] Equally, neither artesunate,[134] nor adjunctive therapies studied have shown evidence of significantly reducing mortality associated with cerebral malaria in trials.[148] There is poor understanding of the biological mechanisms of coma causes, including cerebral malaria, with minimal reports of any improvement in paediatric coma management. The endpoint is often respiratory arrest, usually preceded by seizures.[43,149] Absence of mechanical ventilatory support in sub-Saharan Africa is a substantial factor underpinning static mortality. Simple, affordable, neuroprotective supportive therapeutics are currently under investigation, including aggressive antipyretics,[150] seizure prophylaxis (levetiracetam),[151] non-invasive ventilation, and hypertonic saline (to reduce brain swelling; NCT03300648).

Our meta-analysis concurs with previous reports of high mortality in acute bacterial meningitis.[152] To our knowledge, our study is the first to illustrate that mortality rates associated with coma due to acute bacterial meningitis have not improved over five decades, although the Global Burden of Disease studies has found a disproportionately slower reduction in meningitis mortality in comparison to other vaccine-preventable bacterial syndromes over time,[153] with an increase in ranking of acute bacterial meningitis-related disability in relation to other diseases.[154]

Differences in mortality between causes of non-traumatic coma, such as between cerebral malaria and acute bacterial meningitis, have remained fixed over time in Africa, which probably reflects differing intrinsic disease mechanisms (eg, the neurotropic pathobiology of bacterial meningitis driving irreversible parenchymal brain injury, in contrast to the often-transient effects of malaria that predominate in the neurovasculature which are more easily targeted by intravenous antimalarials). The requirement for lumbar puncture, differences in treatment-seeking behaviours associated with public health messaging, imbalance of curricula delivered to local health-care workers, or a combination of these factors, might contribute to later diagnosis and treatment for acute bacterial meningitis than for cerebral malaria. These factors likely contribute to the higher disability burden and mortality post-discharge (versus in-hospital) identified in non-malarial coma, which is then compounded by the scarcity of neurodisability support in the community.

Geographical region was significantly associated with deaths associated with cerebral malaria on meta-regression analysis. To our knowledge, this has not

previously been described. Our study cannot identify potentially important determinants of differences between regions (eg, seasonality, transmission, healthcare infrastructure). Most studies reporting high mortality from west Africa were published before the millenium, and therefore before many important malaria control programmes were implemented, which might account for some of these differences. Comparisons between high-income European countries and low-income and middle-income countries have identified delays in hospital admission, being underweight or severely anaemic, alongside antimicrobial resistance patterns and vaccine uptake as contributing factors to intercontinental differences in acute bacterial meningitis outcomes. It is likely that such factors have also varied within and between African countries over time, influencing coma outcomes.[155]

The influence of HIV infection increasing mortality rate from non-malarial invasive infection has previously been reported.[40] There are few studies reporting on HIV status in coma, and these studies are therefore not representative of the entire pooled study cohort. Similarly, while we included many cerebral malaria studies, few reported details of key risk factors. For example, metabolic acidosis is consistently reported to be a risk factor for mortality in malaria[35] but was not illustrated here, most likely due to pooled estimates being underpowered to identify a true association.

There are scarce data on disability (including cognitive, motor, visual and hearing impairment, and epilepsy) following non-malarial coma, particularly post-discharge. Studies on cerebral malaria reported heterogeneous proportions of survivors having disability (1–53%), with a pooled estimate of 11% (appendix 4 p 53). This result is considerably lower compared with reports on disability arising from bacterial meningitis.[156] These outcomes might in part reflect the reported propensity of children to fully recover from cerebral malaria.[157] However, more recent longitudinal in-person studies report disability that more severely affects the lives of those affected in up to half of survivors, including in our paired prospective cohort study on febrile coma in Malawi.[45,46,49,66,142] This finding might suggest under-recognition of disability at hospital discharge or in the community in earlier studies, in part due to varying screening practices and capacity but also the late onset of some disabilities (eg, seizures being reported 2 years post-discharge).[46]

Similarly, in patients with coma associated with acute bacterial meningitis, we identified only three studies reporting disability.[20,37,39] Despite the WHO initiative to improve epidemiological and outcome knowledge of acute bacterial meningitis globally, there continues to be a scarcity of disability data on this disease.[158] Implementation of long-term surveillance studies both across the continent and globally are needed, evaluating body function, activity, and participation in acts of daily living.[159] In parallel, there needs to be a growth of disability services to prevent fatal post-discharge complications such as aspiration pneumonia, and to maximise survivors' long-term participation in society.

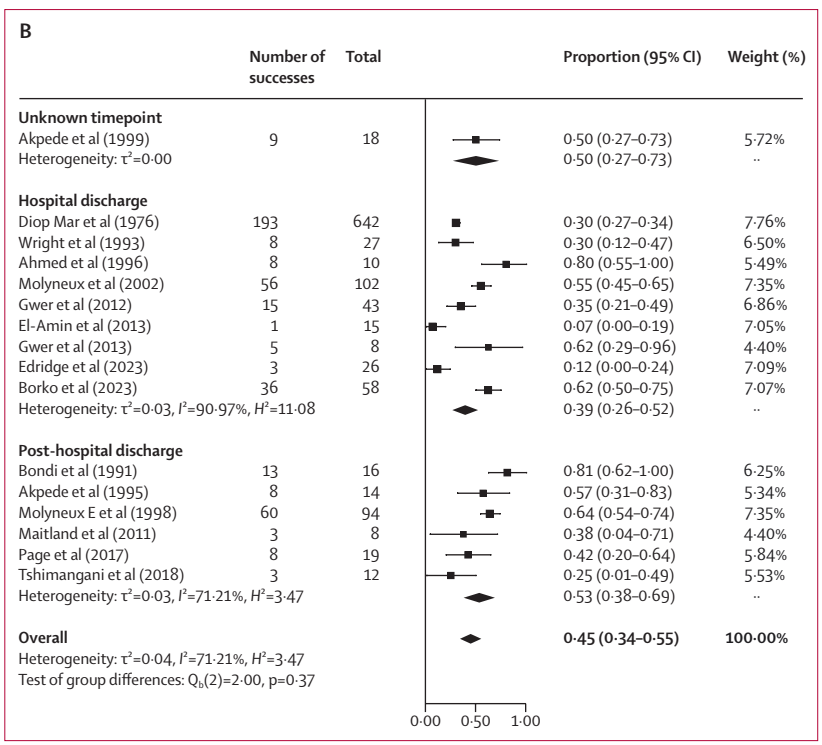

Figure 5: **Forest plot of pooled case-fatality rates of cerebral malaria (A) and acute bacterial meningitis (B) in African children**

(A) Data from 85 studies. (B) Data from 17 studies. The list of included studies can be found in appendix 4 (pp 17–26). CFR=case-fatality rate.

This review is, to our knowledge, the first to date of the mortality and morbidity of all-cause coma and cerebral malaria in sub-Saharan Africa.[6,145] Achieving data-sharing agreements and capturing individual patient data for ten high-quality studies enhanced the detail of data. Limitations include the heterogeneity of studies from a wide temporal and geographical range. Additionally, 36 studies did not use a valid coma tool, further increasing heterogeneity and increasing the risk of bias. Few studies reported on the prevalence of potential clinical predictors of mortality, reflective of the setting of low-income and middle-income countries. Similarly, the few molecular, radiological, and non-infectious diagnostics available in most of the included studies might bias the prevalence estimates of viral CNS infections and toxic, metabolic, and non-infectious causes. There is also likely to be an element of misclassification as causes were taken as reported from studies. Most studies were conducted in large teaching hospitals across Africa, and results might not be generalisable to rural hospitals and primary care facilities.

Overlapping clinical syndromes alongside limited diagnostics in many African settings probably contribute

to the challenges of diagnosing and therefore appropriately managing this critically unwell cohort of children. Recent analyses from leading malaria research centres suggest about a third of children diagnosed with severe malaria are likely to have other undiagnosed non-malarial causes for their severe febrile presentation, and we suspect that many of these cases might have a bacterial cause that is not identified during routine testing.[5,142,160,161] A high bacterial infection burden was identified by molecular testing in our prospective cohort study on febrile coma in Malawi (see paired Article).[142] Prospective research undertaking molecular and radiological diagnostic methods, alongside long-term community-based outcome studies, are required to support the implementation of rigorous diagnostic capacity in Africa and develop pragmatic therapy guidelines.

Despite successful control programmes significantly reducing incidence and mortality from both malaria and bacterial meningitis across the continent,[8,153] our analysis highlights the unacceptable and essentially static high rate of children who continue to present and die from non-traumatic coma in sub-Saharan Africa. A step-change in focus is needed to improve these dismal outcomes. We cannot wait another 50 years simply assuming further reduced disease transmission will eventually reduce coma prevalence and mortality. We need a fundamental shift in direction towards community education to prompt earlier health-seeking behaviour, alongside widening access to specialised care,[131,162–164] and provision of more advanced techniques for coma management akin to those available in high-resource settings. There is an urgent need for increased political strategies and investment, improved health policy making, community awareness, and health service provision to collectively facilitate earlier appropriate referral to specialist centres and optimise the treatment of non-traumatic coma in African children.

Contributors

STJR, CEF, and MJG conceived and designed the systematic review. STJR and CEF developed the search strategy. LJB developed the statistical strategy for the review. STJR and CEF independently assessed titles and abstracts. STJR, CEF, and AB independently assessed full texts of identified studies for eligibility, and performed data extraction and bias assessments. TTa, MR, ELF, DGP, NO, A-LP, EB, EM, AD, ECG, KM, TS, MM, and RI contributed primary data. STJR analysed the data and performed all meta-analyses, with support from MYRH. STJR and CEF prepared tables and figures. STJR, CEF, and MJG wrote the manuscript. STJR, CEF, MJG, KS, DGL, CAM, TTa, GLB, NO, MJG, MN, SBG, and MYRH substantially contributed to the interpretation of the data and commented on the manuscript. All authors have read and approved the final manuscript. All authors had full access to all the data (data verified by STJR, CEF, and MJG) reported in this study and had final responsibility for the decision to submit for publication.

Declaration of interests

DGL, MYRH, and SBG are supported by The Wellcome core award (award number 206545/Z/17/Z) to Malawi–Liverpool–Wellcome Trust. STJR and MN are also supported by Wellcome to conduct paediatric infectious diseases research (203919/Z/16/Z). STJR is also supported by a Thrasher child health early career award, Academy of Medical Sciences starter grant, and European Society of Paediatric Infectious Diseases Society diagnostic grant; and is a Centre for Human Genetics Well Institute Olink-48 grant prize winner and early research career committee member, both at The University of Oxford. MN is also supported by Roche Diagnostics for a Baby and Mother Biomarkers of Infection study; Liverpool School of Tropical Medicine as a clinical fellow for The DIAMONDS Research Consortia; FIND Diagnostics for a literature review on the utility of CRP testing in primary care in low-resource settings for supporting patient management and antibiotic stewardship; is an invited speaker at The Paediatric Infectious Diseases Games; and is deputy convenor, research co-lead, and winter meeting lead at the Royal College Of Paediatrics and Child Health's International Child Health group. MJG is supported to conduct neuroscience and infection research internationally by the Medical Research Council (MRC) Newton Fund (MR/S019960/1), MRC Developmental Pathway Funding Scheme (MR/R015406/1), and National Institute of Health and Care Research (NIHR; 153195 17/60/67, 126156 17/63/11, and 200907). CAM is a UKRI MRC Future Leaders Fellow (MR/V025856/1). TS is supported by the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections (IS-HPU-1112–10117 and NIHR200907), NIHR Global Health Research Group on Brain Infections (17/63/110), the UK MRC Global Effort on COVID-19 Programme (MR/V033441/1), the EU's Horizon 2020 research and innovation programme (ZikaPLAN; 734584), and The Pandemic Institute; receives royalties from Oxford University Press, Liverpool University Press, Cambridge University, and Elsevier for published books he has written on brain infections; co-chaired the Medicines and Healthcare Products Regulatory Agency (MHRA) Expert Working Group on COVID-19 vaccines between 2020 and 2023; was a member of the COVID-19 Vaccines Benefit Risk Expert working group for the Commission on Human Medicines (CHM) committee of MHRA between 2020 and 2023; is a Committee Member of the Wellcome Trust Pathogen Biology and Disease Transmission Discovery advisory group; was a member of the MRC's Infections and Immunity Board between 2018 and 2022; sat on the Research Excellence Framework Panel between 2021 and 2022; and was on the data safety monitoring committee of the GSK Study to Evaluate the Safety and Immunogenicity of a Candidate Ebola Vaccine in Children (ChAd3 EBO-Z) vaccine (GSK3390107A). BDM is supported for COVID-19 neuroscience research by UK Research and Innovation (UKRI) and MRC (MR/V03605X/1); and for additional neurological inflammation due to viral infection research by grants from the MRC and UKRI (MR/V007181/1), MRC (MR/T028750/1), and the Wellcome Trust (ISSF201902/3). TTa is supported by a research grant from the US National Institutes of Health (NIH); is the President-Elect for the American Society of Tropical Medicine and Hygiene; and is a member of the Malaria Advisory Council for Novartis Pharma. GB is supported by two active and two recent research grants from US NIH; consults on educational materials for Neurotorium, Temp Traq, and similar devices at Blue Spark Technologies; lectures for The University of Calgary; participates on an advisory board for the BRIDGE clinical trial; and is on the editorial board of the *Lancet Neurology*, Neurotorium, and Zambian League against Epilepsy. ECG is funded by the MRC as core support to the Medical Research Council Clinical Trials Unit at University College London (MC_UU_00004/05). STJR, BDM, and TS are members of the Encephalitis International Scientific Advisory Panel—BDM is Scientific Chair and TS is President. All other authors declare no competing interests.

Data sharing

Data can be requested from STJR and CF after publication of this study. De-identified participant data, data dictionary, and other specified datasets can be requested. The study protocol is published and available open access online and includes the statistical analysis plan. Specific requests for data will require the submission of a proposal with a valuable research question as assessed by the study team. A data access agreement should be signed.

Acknowledgments

We thank our all our collaborators and their research institutes (Universities of Oxford [MORU], College London, and Liverpool); Malaria Blantyre Project; and Médecins Sans Frontières epicentre, for data-sharing agreements that substantially enhance the quality of the study estimates.

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