Aetiology and Outcome of Non-Traumatic Coma in African Children: Protocol for a Systematic Review and Meta-Analysis

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Protocol

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Abstract

Background: Non-traumatic coma is a common acute childhood presentation to healthcare facilities in Africa and is associated with high morbidity and mortality. Historically, the majority of cases were attributed to cerebral malaria (CM). With the recent drastic reduction in malaria incidence, non-malarial coma is becoming a larger proportion of cases and determining the aetiology is diagnostically challenging, particularly in resource-limited settings. The purpose of this study will be to evaluate the aetiology and prognosis of non-traumatic coma in African children.

Methods: From inception onwards, systematic searches of MEDLINE, Embase, and Scopus, will identify prospective and retrospective studies (including randomised controlled trials, cluster randomised trials, cohort studies, cross-sectional, and case-control studies) recruiting children (1 month-16 years) with non-traumatic coma (defined by Blantyre Coma Score ≤2 or comparable alternative) from any African country. Disease-specific studies will be included given that coma is associated and reported. The primary outcome is to determine the aetiology (infectious and non-infectious) of non-traumatic coma in African children, with pooled prevalence estimates of causes (e.g. malaria). Secondary outcomes are to determine overall estimates of morbidity and mortality of all cause non-traumatic coma and disease-specific states of non-traumatic coma, where available. Random effects meta-analysis will summarize aetiology data and in-hospital and post-discharge mortality. Heterogeneity will be quantified with $\tau 2$, I2, and Cochran's Q test.

Discussion: This systematic review will provide a summary of the best available evidence on the aetiology and outcome of non-traumatic coma in African children.

Systematic Review Registration: This review is registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42020141937).

Background

Non-traumatic coma is a common acute childhood presentation to healthcare facilities throughout Africa. Infectious causes of deep coma (defined as Blantyre Coma Scale (BCS) ≤ 2) include cerebral malaria (CM), acute bacterial meningitis (ABM), viral encephalitides, and HIV-associated opportunistic pathogens, such as tuberculosis and cryptococcal disease, and non-infectious causes include metabolic abnormalities and toxins.(1–3) In malaria-endemic regions, CM is diagnosed in children with coma and peripheral malaria parasitaemia with no other identifiable cause.(1) Limited diagnostic resources in many African settings and the phenomenon of asymptomatic malaria parasitaemia have rendered the alternate diagnoses of childhood coma under-described, resulting in a poor epidemiological understanding of this clinical presentation.(4, 5) A study in Kenya revealed that less than half of children admitted with acute non-traumatic coma had an identified cause.(6) With the recent drastic reduction in malaria incidence, it is postulated that non-malarial coma represents a larger proportion of coma cases.(6) Non-traumatic coma in children is associated with high mortality (15–58%) and significant neurological sequelae (31–

68%).(7–9) The long-term effects of coma on cognition and educational achievement is less commonly described, and existing literature primarily focuses on CM.(10, 11) These effects play an important role in the socioeconomic development of low-resource countries.(12)

There is a paucity of data on the aetiology of non-malarial coma in Africa.(3) Given the high burden of morbidity and mortality associated with this clinical presentation, an overview of the literature to date is vital to direct further research. Gwer *et al.* (2013) performed a literature review of fourteen single studies on childhood non-traumatic coma in Africa and Asia.(9) This is the only existing review investigating childhood non-traumatic coma in Africa, and it does not include a formal outcome analysis nor meta-analysis (on aetiology nor outcome). The review also focused on all-cause non-traumatic coma studies and did not explore severe coma subgroups in single disease and/or pathogen studies for outcome. Moreover, since this literature review, there have subsequently been a number of larger important studies using molecular diagnostics and other adjuvant diagnostic capacities, such as magnetic resonance imaging (MRI) and electroencephalogram (EEG). Non-traumatic coma outcomes in Africa are heterogenous between studies, and long-term follow-up is sparse. A systematic review and meta-analysis on aetiology and outcome of paediatric non-traumatic coma in Africa is needed; it will substantially enrich accurate estimates of both the proportions of individual causes of non-traumatic coma and their associated morbidity and mortality.

Using an adapted Population, Intervention, Comparator, Outcome, and Study Designs (PICOS) framework, we will examine the best available evidence on the aetiology of acute non-traumatic coma in African children, including specific syndromic cohorts in comatose children to broaden the search of studies and maximise the evidence base.(13) Our adapted framework will use the Population (children with non-traumatic coma), Exposure (aetiology of infection and covariates, e.g. HIV status and malnutrition), Outcome (morbidity and mortality), and Study Design framework. In this systematic review and meta-analysis, we will consider all types of studies and extract data that fits with our inclusion criteria. We will estimate the morbidity and mortality of all-cause non-traumatic coma and disease-specific coma in the African setting. Lastly, we will suggest directions for future research in this important, under-researched area.

Methods/design

Study Design

This is a systematic review and meta-analysis seeking to evaluate the aetiology and prognosis of non-traumatic coma in African children.

Protocol Development and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) was used to develop this protocol (Table 1), and we will use elements of the Cochrane Handbook of Systematic Reviews to guide the systematic review.(14, 15) An adapted Population, Intervention,

Comparator, Outcome and Study Designs (PICOS) framework was used to develop the inclusion and exclusion criteria.(13) This review is registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42020141937).

Table 1
PRISMA-P Checklist

Section/Topic	#	Checklist Item	Information Reported		Line Number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	Yes		1–2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		No	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	Yes		4
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes		7–37
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes		324–328
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		No	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	Yes		318–321
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes		320–321
Role of Sponsor/ Funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes		320–321
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes		98–129

Section/Topic	#	Checklist Item	Information Reported		Line Number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes		131–140
METHODS					
Eligibility Criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	Yes		163–171
Information Sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Yes		174–182
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes		Table 2 (Appendix)
STUDY RECORDS					
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes		180–182
Selection Process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	Yes		185–196
Data Collection Process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes		199–226
Data Items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes		212–226; Appendix A
Outcomes and Prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes		156–160; 207–210

Section/Topic	#	Checklist Item	Information Reported		Line Number(s)
			Yes	No	
Risk of Bias in Individual Studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes		229–241
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes		244–267
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	Yes		244–267
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	Yes		261–266
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		No	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	Yes		248–261
Confidence in Cumulative Evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	Yes		238–241

Outcomes of Interest

The primary outcome of this study is to determine the aetiology (infectious and non-infectious) of non-traumatic coma in African children, with pooled prevalence estimates of causes (e.g. malaria). The secondary outcomes are to determine the overall estimates of morbidity and mortality of all-cause non-traumatic coma and disease-specific states of non-traumatic coma, where available. These outcomes will provide critical data needed to inform future directions in research.

Eligibility Criteria

Systematic searches, using multiple databases (see below) from inception will identify prospective and retrospective studies (randomised controlled trials, cluster randomised trials, cohort studies, cross-sectional, and case-control studies) recruiting children (1 month-16 years) with non-traumatic coma

(defined by Blantyre Coma Score ≤ 2 or comparable alternative) from any African country. Disease-specific studies (e.g. malaria) will be included given that coma is associated and reported. Case reports, case series, commentaries, and editorials will be excluded from the review, and we will exclude all publications that do not contain primary data. This rationale for such a broad geographical and aetiological eligibility is to ensure the most comprehensive investigation and analysis of non-traumatic coma (including disease specific studies) in African children to date.

Electronic Search Strategy

We will search the MEDLINE, Embase, and Scopus databases from inception onwards with no date limits. The complete MEDLINE search strategy is included in Table 2. Searches will be limited to English and French articles. We will search conference proceedings and databases of ongoing studies to identify studies not found in the databases listed above; grey literature will not be included. When appropriate, attempts to contact study authors for primary data will be made. Reference lists of eligible studies and relevant systematic reviews will be searched to identify additional studies to be considered for inclusion. All records identified from the search will be imported to EndNote X9.3.1 (Clarivate Analytics, Philadelphia, PA), a citation management programme, following which duplicates will be removed.

Table 2
MEDLINE Search Strategy*

Number	Search terms
1	Coma* OR consciousness OR unconscious OR “non-traumatic coma” OR “non traumatic coma” OR “nontraumatic coma” OR encephalopathy OR “febrile encephalopathy” NOT “head injury”
2	aetiology OR aetiologies OR etiology OR etiologies OR cause OR causes OR causality
3	Paediatric OR pediatric OR child*
4	Africa OR “sub Saharan Africa” OR “sub-Saharan Africa” OR Algeria OR Angola OR Benin OR Botswana OR “Burkina Faso” OR Burundi OR Cameroon OR “Cape Verde” OR “Central African Republic” OR Chad OR Comoros OR “Republic of the Congo” OR “Democratic Republic of the Congo” OR “Cote d’Ivoire" OR Djibouti OR Egypt OR “Equatorial Guinea” OR Eritrea OR Eswatini OR Ethiopia OR Gabon OR “The Gambia” OR Ghana OR Guinea OR “Guinea-Bissau" OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR “Sao Tome and Principe” OR Senegal OR Seychelles OR “Sierra Leone” OR Somalia OR “South Africa” OR “South Sudan” OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe
5	#1 AND #2 AND #3 AND #4
*Search was limited to English and French; timeline from inception onwards with no date restrictions.	

Screening and Selection Criteria

Two authors (SR and CF) will independently screen the title and abstract of each publication, and disagreements will be resolved by consensus. References for which the full text is reviewed will include: (1) a mention of coma, children (1 month-16 years) and non-traumatic aetiology and (2) recruitment in an African setting for which it is possible to disaggregate a total number of children with non-traumatic coma and possible to extract aetiology or outcome data. Those articles obviously irrelevant to the review or which do not clearly meet the inclusion criteria will be excluded. The number of records screened and excluded will be recorded.

The full text of the identified studies will be individually assessed for eligibility against the predetermined criteria by two reviewers (two out of CF, SR, and AB for each article) in duplicate, with disagreements resolved by consensus. Reasons for exclusion of full-text articles will be documented.

Data Extraction

We will use the Cochrane Effective Practice and Organisation of Care (EPOC) standard data collection form and adapt it for study characteristics and outcome data.(17) Two review authors will pilot the form on a randomly selected subset of 10% of included studies.(15, 18) Reviewers will extract data independently and in duplicate from each eligible study. Any disagreements will be resolved by consensus or discussed with a fourth reviewer (MG) if consensus is not achieved. Attempts to contact authors will be made to obtain missing outcome data or other key study characteristics. The full data extraction form can be found in Appendix A.

The primary outcome has been defined as the aetiology of non-traumatic coma, including syndromic diagnosis and the identification of causative pathogens. Secondary outcomes include mortality rates and neurodisability, stratified with both the clinical syndromes and causative pathogens.

The following information will be extracted from each included trial:

(1) Author and Publication Details: Name of first author, corresponding author, publication year and journal, PubMed and registration ID, and funding source.

(2) Study Characteristics: Study design, duration, location(s), setting, timing of data collection (prospective or retrospective), methods of recruitment, duration of follow-up and statistical methods, completeness of outcome data, and Cochrane variables of bias.(16)

(3) Participants: Number, age range, mean age, gender, definition of coma, inclusion and exclusion criteria, withdrawals and exclusions, method of diagnosis (microbiological methods used, including culture and polymerase chain reaction (PCR) methods), comorbidities, and other relevant characteristics, such as human immunodeficiency virus (HIV) and nutritional status.

(4) Outcome: Clinical diagnosis, microbiological diagnosis, clinical outcome, such as fatality or neurological and/or neurocognitive sequelae for each clinical syndrome, and microbiological diagnosis.

Neurological sequelae stratified into subtypes including motor, vision, hearing, epilepsy, and cognitive-behavioural.

Assessment of Risk of Bias

Three reviewers (CF, SR, and AB) will independently conduct a bias risk assessment at the outcome and study-level to assess the quality of included studies. The validated Cochrane Collaboration Risk of Bias tool will be used as a framework upon which to guide quality assessments for randomised-controlled trials.(16) A modified Newcastle-Ottawa Scale (NOS), which incorporates the Critical Appraisal Skills Programme (CASP) checklist (a non-validated tool) and Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) (a validated tool), will be used for all other study types (Appendix B).(19, 20) Risk of bias for each domain will be recorded as high (1), low (0), or unclear. Any disagreements will be resolved by consensus or discussed with a fourth reviewer (MG) if consensus is not achieved. The risk of bias for included studies will be described throughout data synthesis. Lastly, since there is no gold standard to assess risk of bias for observational studies, the modified NOS will be used to assess the strength of the body of evidence. The NOS is a commonly used tool for meta-analysis that, despite its limitations (including subjectivity), will best capture risk of bias in our study cohort.

Data Synthesis

A narrative synthesis of the data will also be provided, including a summary and explanation of characteristics and key summary tables and findings of included studies per outcome. For aetiology analyses, we will include all studies regardless of coma definition, and we will include usual care and intervention arms of RCTs. Heterogeneity will be quantified with $\tau 2$, I2, and Cochran's Q test.(15) Aetiology data will be summarised by random effects meta-analysis. Because of concerns about meta-analysis of proportions on very heterogeneous populations, we also plan a meta-analysis of outcome stratified by inclusion criteria (e.g. coma measure). Mortality will be presented as a simple proportion with exact binomial confidence intervals, and pooled mortality estimates will be calculated using generalised linear mixed models (a normal-binomial model). For interventional studies, the outcomes in the usual care arm of the study only will be included in these estimates. There will also be a random effects meta-analysis of in-hospital and post-discharge mortality. Exploratory meta-regression will be undertaken to explore heterogeneity by including covariates as fixed effects (e.g. proportion of patients infected with HIV and malnutrition) and testing for improved model fit by likelihood ratio testing of nested models. A p-value of < 0.05 will be considered a statistically significantly improved fit. Summary estimates of one-month mortality, where available, will be considered together and presented in the same way. Pooled prevalence estimates of malaria, acute bacterial or viral meningitis, encephalitis, and bloodstream infection will be calculated using random effects meta-analysis as above. Subgroup analyses will include meta-analysis of severe coma (very low coma score on admission), less severe coma (higher coma score on admission) and disease-specific aetiologies (malaria, bacterial meningitis, viral meningitis or encephalitis, or blood stream infection). Separately, a sensitivity analysis will be performed at the outcome-level using only high-quality studies.(15) High-quality studies – those graded low risk of bias across all domains – will be defined for each study type. We will provide a table of study characteristics.

Discussion

This systematic review will be published in accordance with PRISMA-P guidelines, and the review process will be recorded through use of the PRISMA-P flow diagram.(21) In the event of protocol amendments, a description of the change and rationale will be documented with the journal, with the date of amendment.

There are some practical issues and limitations of our review. At the study-level, it will not always be possible to confidently ascertain depth of coma in these children, as a valid coma scale (e.g. Glasgow Coma Scale (GCS), BCS) is not always used in studies. At the review-level, more papers will likely be set in research centres and university hospitals, and fewer papers will be set at rural and district hospitals and clinics. Due to the endemicity of infectious febrile coma aetiologies (e.g. CM, ABM), more papers will likely be set in sub-Saharan Africa than North Africa. Together, these may lead to urban and regional biases. Lastly, included studies are limited to English and French, which may exclude papers written in other languages spoken throughout the continent.

This systematic review and meta-analysis will provide a transparent review of the available evidence to provide a more accurate understanding of the causes and outcomes of non-traumatic coma in African children. We seek to publish our results in a peer-reviewed journal, attend conferences, and inform relevant parties in the field of our findings. We hope that this review will raise awareness of this common presentation in African settings. This review will highlight gaps in the literature and areas in which future research is required.

Abbreviations

CM: cerebral malaria

ABM: acute bacterial meningitis

MRI: magnetic resonance imaging

EEG: electroencephalogram

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

PICOS: Population, Intervention, Comparator, Outcome, and Study Designs

PCR: polymerase chain reaction

HIV: human immunodeficiency virus

EPOC: Effective Practice and Organisation of Care

NOS: Newcastle-Ottawa Scale

CASP: Critical Appraisal Skills Programme

Declarations

Ethics Approach and Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability of Data and Materials

Not applicable

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

SR, MG, and CF conceived and designed the systematic review. SR and CF developed the search strategy, and LB developed the statistical strategy for the review. CF and AB drafted the protocol manuscript, and SR, KBS, MG and LB contributed to the critical revision of the manuscript for methodological and intellectual content. SR is the guarantor of the review. All authors approved the final version of the submitted manuscript.

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Amendments

In the event of protocol amendments, a description of the change and rationale will be documented with the date of amendment.

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Supplementary Files

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

- APPENDIX.docx
- AppendixADataExtractionForm.docx
- AppendixBModifiedNewcastleOttawaScale.docx