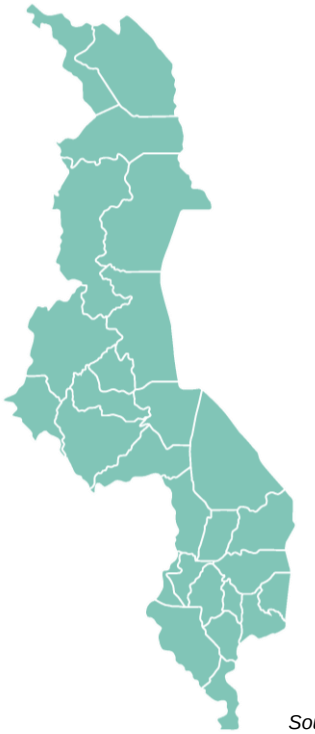
The Infectious Etiology of Non-Traumatic Coma in Children in Malawi



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ABBREVIATIONS

Abbreviation	Explanation
ABM	Acute Bacterial Meningitis
A&E	Accident & Emergency department
BCS	Blantyre Coma Scale
CM	Cerebral malaria
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
EBV	Epstein-Bar virus
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HSV	Human simplex virus
PCR	Polymerase chain reaction
P. falciparum	Plasmodium falciparum
RDT	Rapid diagnostic test
USA	United States of America
SSPE	Subacute sclerosing pan encephalitis
WHO	World Health Organization

ABSTRACT

Introduction: Acute non-traumatic coma (NTC) is a common reason for hospital admission in children in low-income countries. Cerebral malaria was always thought to be one of the main causes of NTC. Now the malaria rate has declined of the past twenty years, it has become clear that numerous other illnesses causing NTC are also of great importance.

Objective: To identify the etiology of infectious non-traumatic coma in 49 Malawian children in the Queen Elizabeth Hospital from a cohort study conducted in 2015. By determining the likelihood of cerebral malaria and secondly identifying potential bacterial and viral alternative etiologies.

Methods: A literature search was conducted to identify the range of etiologies causing NTC in children in sub-Saharan Africa and to develop a diagnostic algorithm to categorize the children on probability of having cerebral malaria. This algorithm was applied to the cohort of Malawian children from 2015. Subsequently, the likelihood of having an alternative etiology was evaluated in this cohort based on clinical and laboratory data. Lastly, the data from the Malawian cohort were compared to studies identified by the initial literature search.

Results: The literature showed that malaria remains one of the most common causes of non-traumatic coma. Followed by bacterial and viral respectively. In the Malawian cohort, 63.3% of the children had a confirmed cerebral malaria, 6.1% a high probability, 20.4% a medium probability and 6.1% a low probability. In thirteen children a medium or low probability of bacterial meningitis was determined, and no confirmed bacterial meningitis. Four possible viral causes were determined. Bacterial and viral causes were randomly distributed over the five malaria groups.

Conclusion: Differentiating between bacterial, viral or malarial causes of NTC based on clinical data and basic laboratory results, remains a challenge. Further research on and improved control of malaria and other infections should help to develop interventions to combat non-traumatic coma in children.

SAMENVATTING

Introductie: Acute non-traumatische coma (NTC) is een veelvoorkomende oorzaak van ziekenhuisopname in ontwikkelingslanden. Er werd altijd gedacht dat cerebrale malaria een van de voornaamste oorzaken van NTC is. Nu de malaria graad is afgenomen over de afgelopen twintig jaar, is het duidelijk geworden dat veel andere ziektes die NTC veroorzaken ook van belang zijn.

Objectief: Het identificeren van de etiologie van infectieuze non-traumatische coma in 49 Malawische kinderen in het Queen Elizabeth ziekenhuis, van een cohort studie uitgevoerd in 2015. Door het bepalen van de waarschijnlijkheid van cerebrale malaria en ten tweede het identificeren van potentiële bacteriële en virale alternatieve ethologiën.

Methoden: Een literatuur zoekopdracht werd uitgevoerd om de verschillende ethologiën die NTC veroorzaken te bepalen in kinderen in sub-Sahara Afrika en een diagnostisch algoritme was ontwikkeld om de kinderen te categoriseren op de waarschijnlijkheid dat ze cerebrale malaria hebben. Dit algoritme werd toegepast op het cohort van Malawische kinderen van 2015. Verder werd de waarschijnlijkheid van het hebben van een alternatieve etiologie geanalyseerd in dit cohort gebaseerd op klinische en laboratorium data. Ten slotte, werd de data van het cohort uit Malawi vergeleken met de onderzoeken van de literatuur zoekopdracht.

Resultaten: De literatuur liet zien dat malaria nog steeds een van de belangrijkste oorzaken van non-traumatische coma is. Gevolgd door bacteriële en virale oorzaken respectievelijk. In het cohort van Malawi had 63.3% van de kinderen een ‘bevestigde cerebrale malaria’, 6.1% een ‘hoge waarschijnlijkheid’, 20.4% een ‘medium waarschijnlijkheid’ en 6.1% een ‘lage waarschijnlijkheid’. In dertien kinderen werd een medium of lage waarschijnlijkheid van bacteriële meningitis gevonden, en geen bevestigde bacteriële meningitis. Vier mogelijke virale oorzaken werden gevonden. Bacteriële en virale oorzaken waren willekeurig verdeeld over de vijf malaria groepen.

Conclusie: Differentiëren tussen bacteriële, virale oorzaken of malaria als oorzaak van NTC gebaseerd op klinische data en basale laboratorium testen, blijft een uitdaging. Verder onderzoek en verbeterde controle van malaria en andere infecties zouden moeten helpen bij het ontwikkelen van interventies om non-traumatische coma in kinderen de kop in te drukken.

Acute non-traumatic coma (NTC) is an important reason for hospital admission in children in developing countries (Macpherson Mallewa P. V., 2013). The most common causes of impaired consciousness are cerebral malaria (CM), acute bacterial meningitis (ABM) (J. A. Berkley, 1999) and viral encephalitides (Samson Gwer N. T., 2012). Among these children there is a high mortality (between 15% and 58%) (Samson Gwer C. C., 2013), and there is a high risk of neurological sequelae in survivors (J. A. Berkley, 1999) and (Samson Gwer N. T., 2012) (between 31% to 67%). These outcomes are highly dependent on the cause of the non-traumatic coma (C P Wong, 2001).

Cerebral malaria (CM) is often considered as the most important cause of non-traumatic coma in malaria-endemic areas like Malawi (Samson Gwer C. R., 2007). It is the most severe manifestation of *Plasmodium falciparum*, which can cause sequestration of infected erythrocytes, followed by the clogging of mainly the small blood vessels. As a result, the oxygen rich blood supply will not reach some parts of the body, which can damage organs or cells. (Terrie E Taylor, 2004). With cerebral malaria this happens in the vessels of the brain, which can cause non-traumatic coma. Children below five are mainly affected and primarily in Sub-Saharan Africa, where the most transmission of malaria occurs (World Health Organization, 2000).

Cerebral malaria can be diagnosed with an autopsy of the brain. If patients need treatment, they can be clinically diagnosed with cerebral malaria when they have an unarousable coma (Blantyre Coma Scale (BCS) < 3 in children) that is not attributable to another cause and have asexual forms of *P. falciparum* parasitemia in their blood (Terrie E Taylor, 2004) (Macpherson Mallewa P. V., 2013). But these diagnostic criteria are less accurate (Terrie E Taylor, 2004). Furthermore, retinopathy is an important occurrence for the diagnosis of cerebral malaria (Valerie A. White, 2009). The non-perfusion of the retinal capillaries due to the clogging of the vessels (which also happens in the brain with cerebral malaria) can be seen in the retina of the eye. The presence of retinopathy makes it very likely that the patient is infected with malaria. Rate of retinal hemorrhages in patients with clinically defined cerebral malaria is 40-60% (Valerie A. White, 2009).

Therefore, sufficient laboratory resources and experienced clinicians, to determine retinopathy, are necessary to detect malaria and find asexual forms of malaria in the blood. Furthermore other possible causes need to be excluded. In developing countries these laboratory resources are not always present, nor are there enough clinicians to perform the

diagnostic testing. Moreover, when it is possible to perform the diagnostic testing that is needed, patients may happen to be malaria parasitemic but this is not the cause of the non-traumatic coma (Samson Gwer C. R., 2007). To distinguish malaria as a cause or as a asymptomatic carrier, therefore, is not that easy. And lastly, the clinical presentations of the different illnesses that can cause non-traumatic coma are very similar. But because these children life in malaria-endemic areas, physicians tend to diagnose the children with cerebral malaria, rather than another cause. As a result, a sufficient amount of children is over-diagnosed with cerebral malaria (Samson Gwer C. R., 2007).

Over the past few years there has been a decline in the malaria transmission and incidence, followed by a decline in the prevalence of non-traumatic coma in children. Controversially, this is accompanied by a rise in the number of children presenting with non-traumatic coma due to an undetermined cause (Samson Gwer N. T., 2012). This increase can be due to new etiologies or can consist of etiologies that were always present but over-diagnosed with cerebral malaria. In an autopsy study, 23% of the children with clinically defined cerebral malaria had actually died from other causes (Terrie E Taylor, 2004), like Reye syndrome, ruptured arteriovenous malformation, hepatic necrosis and bacterial meningitis. Moreover, in another study, the cerebrospinal fluid of 49 Malawian children diagnosed with cerebral malaria according to the World Health Organization (WHO) definition was investigated and found that 9% of the children had a Herpes simplex type 1 infection (Christian D. Schubart, 2006). Little attention has been paid to the other possible illnesses that cause non-traumatic coma, therefore it is important to find and investigate these other causes.

Collecting data about the etiology of the illnesses that cause the coma will make it possible to take definitive steps in combating these diseases, such as preventative measures and targeted treatment. A decline in the number coma causing conditions will reduce the mortality rate and the amount of long-term neurologic sequalae. The aim of this thesis is to identify the etiology of infectious non-traumatic coma in 49 Malawian children in the Queen Elizabeth Hospital from a cohort study conducted in 2015. More specifically, I will first do a literature search for articles focusing on children with non-traumatic coma in developing countries to give an overview of the magnitude of the malarial, bacterial and viral causes of non-traumatic coma. Secondly I will develop and implement a diagnostic algorithm to determine the likelihood of a cerebral malarial cause in the 49 Malawian children. Thirdly, I will identify the potential bacterial and viral alternative etiologies in these children based on clinical data and laboratory diagnostic results. Lastly, I will compare the results from this dataset to datasets with other cohorts of children with non-traumatic coma in Malawi and other Sub-Saharan, low-income or malaria-endemic countries, as identified by my literature search.

METHODS

DATA COLLECTION

To answer the first part of the research question a literature search was conducted using PubMed to search for studies which reported on children with non-traumatic coma in low-income countries. The aim for the search is to find articles which report on the etiologies of non-traumatic coma in children, to give an overview of the magnitude of the malarial, bacterial and viral causes of non-traumatic coma and compare this data with the identified etiologies from the 49 Malawian children. The following search phrase was used:

(child[Title] OR children[Title] OR childhood[Title] OR pediatric[Title] OR paediatric[Title] OR pre-school[Title]) **AND** (cerebral malaria[Title] OR convulsion[Title] OR seizure[Title] OR non-traumatic coma[Title] OR CNS infection[Title] OR central nervous system infection[Title] OR encephalitis[Title] OR coma[Title] OR comatose[Title] OR impaired consciousness[Title] OR encephalitides[Title]) **AND** (developing countries[Title/Abstract] OR developing country[Title/Abstract] OR developing world[Title/Abstract] OR resource-poor countries[Title/Abstract] OR resource-poor country[Title/Abstract] OR resource-poor setting[Title/Abstract] OR low-income country[Title/Abstract] OR low-income countries[Title/Abstract] OR low-income setting[Title/Abstract] OR malaria-endemic region[Title/Abstract] OR malaria-endemic area[Title/Abstract] OR Sub-Saharan Africa[Title/Abstract] OR Africa[Title/Abstract] OR Malawi[Title/Abstract] OR Malawian[Title/Abstract]).

The search consists of three parts. The first part focusses on the age group of the population, children, which can be found in the title of the publications because it is of major importance. The second part focusses on ‘coma’ and ‘convulsions’, which can be found in the title. ‘Cerebral malaria’ was also included to find records that are concentrating on the problem of the over-diagnosing of cerebral malaria. These studies may also provide different causes of non-traumatic coma. The last part of the search describes the place where the studies were conducted. During the conduction of a preliminary search, only a handful of studies from Malawi were obtained, I therefore decided to also search for publications from other countries that are comparable with Malawi. Comparable countries are countries from the same income group (low-income), countries from the same continent (Sub-Saharan Africa) or malaria-endemic countries. This can be found in the title or abstract of the different studies. These terms are not always stated in the title, therefore the abstract was also considered.

Inclusion criteria

- Age six months – eighteen years: The age of the children from the dataset in Malawi reaches from eight months up till thirteen years. Children were included in the dataset between the age of six months up till eighteen years. The same inclusion criteria were chosen for the literature analysis. Children younger than six months were excluded because they are not comparable with older children. They have a less developed immune-system, therefore making them more susceptible for different and more diseases (A. Katharina Simon, 2015).
- Non-traumatic cause: Coma and convulsions must be due to a non-traumatic cause, since the children from the dataset were also included if they had a non-traumatic coma. If the authors of the publications stated the cause of coma or convulsions as non-traumatic this was considered sufficient. It was not chosen to use a specific inclusion criterium (like BCS ≤ 2) because there is a lot of heterogenicity between the inclusion criteria of the different studies, which would result in the loss of some studies.
- Comparable country:
    - Malawi is defined as a *low-income country* by The World Bank. To compare the data found in the articles with the data retrieved from the Malawi dataset, the countries in the literature also have to be low-income. These countries deal with similar problems, for example diagnostic difficulties due to low-resources. It was sufficient if the study itself defined the country as a low-income country.
    - Malawi is located in *Sub-Saharan Africa*. Countries that are also in Sub-Saharan Africa are comparable with Malawi.
    - Malawi is *malaria endemic*. Countries that are also malaria-endemic are comparable with Malawi, since they also have a high prevalence of malaria.
- Published after 1995: Article is published in 1995 or after. The malaria transmission has declined (World Health Organization, 2000) in a lot of countries. But still there are malaria-endemic areas where cerebral malaria is thought to be the most common cause of non-traumatic coma in children. All articles published in this period are included, so also records from countries where they consider malaria still the number one cause. If only records are included from after the malaria-decline, there would not have been enough data.
- Etiology: Article focusses on the etiology of non-traumatic coma or convulsions, or questions the diagnosis non-traumatic coma due to cerebral malaria.
- Primary data: To prevent that data from the same study are used twice.

Exclusion criteria

- Seizures in the context of epilepsy: Articles that focus on seizures within the context of epilepsy are excluded. These kind of seizures are not relevant to retrieve data about, because this thesis focusses on the etiology of coma with febrile illnesses.
- Study population of less than forty children: Publications who studied a group of children consisting of less than forty children were excluded. These studies are not considered to contain useable data.

CRITICAL APPRAISAL

The articles retrieved were all critically appraised with a critical appraisal tool based on the Critical Appraisal Checklists found on the Joanna Briggs Institute to ensure sufficient quality of the records.

LITERATURE DATA EXTRACTION

The articles included from the PubMed search were analyzed on the prevalence of malaria. This is to give an overview of the magnitude of the malarial, bacterial and viral causes of non-traumatic coma, and secondly to compare these numbers with the dataset. The specific viral and bacterial infections were also stated, if they were mentioned in the different records. The number of unknown causes are also established, to put the findings into perspective.

DATASET DESCRIPTION

The clinical cohort study was conducted in the Queen Elizabeth Central Hospital in Blantyre, Malawi, from 2015 to 2016. Children with non-traumatic coma between the ages of six months and eighteen years were included when they presented to the emergency ward. All clinical (history of present illness, medical history, symptoms, results from physical examination, results from diagnostics, outcome, etc.), were collected during admission. Children suspected of a clinical meningitis (fever, stiff neck, cerebrospinal fluid white blood cell count >100 cells/mm^3) were excluded. All data were captured in an online Castor database. This data was retrieved from Castor and exported into Excel, where the analyses for this thesis took place.

The first analysis of the dataset consisted of determining the baseline characteristics, symptoms and outcomes. Data from the Dataset in Castor were exported in Excel, where the analysis took place.

Secondly, a clinical algorithm was developed for the probability of the diagnosis cerebral malaria. This algorithm was based on the results of the following tests: the presence of retinopathy, thick peripheral blood smear (slide) and the rapid diagnostic test (RDT). Based on these results the patients were categorized into five groups: 'confirmed cerebral malaria', 'high probability', 'medium probability', 'low probability' and 'no cerebral malaria. Criteria for the different groups are stated in table 1.

Table 1 – Diagnostic Criteria for the Probability of Cerebral Malaria for Children with a BCS ≤ 2

Confirmed	High probability	Medium probability	Low probability	No Cerebral Malaria
• Retinopathy positive • Slide positive at A&E of Admission	• Retinopathy positive • Slide or RDT unknown or negative at A&E or Admission	• Retinopathy negative • Slide positive at A&E or Admission	• Retinopathy negative • Only RDT positive at previous RDT, A&E or Admission	• Retinopathy negative • RDT and slide negative at previous RDT, A&E and Admission

Retinopathy: a positive test means that retinopathy is present.
Slide: thick peripheral blood smear.
RDT: rapid diagnostic test.
A&E: Accident & Emergency Department.

A confirmed cerebral malaria was considered in children with a positive retinopathy and slide. This is because retinopathy is the most specific clinical sign, in an autopsy study in Malawi (Terrie E Taylor, 2004) they found that retinopathy was the strongest predictor to differentiate between a malarial and non-malarial coma. For high probability a positive retinopathy was sufficient enough. This is because some patients did not have a positive slide or RDT at admission or at the emergency department (A&E) anymore because they were already treated with antimalarial drugs which resulted in a negative slide or negative RDT. Since the finding of retinopathy is very specific for cerebral malaria, this result only was sufficient enough for an high possibility of cerebral malaria. Medium probability is found in patients with a positive slide at A&E or admission. The finding of malaria parasites in the blood only is not sufficient to diagnose children with a confirmed or high cerebral malaria, because in a retrospective analysis in Kenya they found that 4% of the children who were unconscious and had malaria parasites in their blood also had definite bacterial meningitis (J. A. Berkley, 1999). The lowest probability of cerebral malaria was found in children with only a positive RDT. This makes cerebral malaria less likely since a RDT test can remain positive for a long period after a patient recovered from malaria (Ursula Dalrymple, 2018). No cerebral malaria is diagnosed when all of the tests, including retinopathy, their results are negative.

For the third part of the research question: identifying the potential bacterial and viral alternative etiologies in the 49 Malawian children, the results of the following tests were extracted from the Castor database: body temperature, the blood and cerebrospinal fluid glucose, the white blood cell count, blood culture, cerebrospinal fluid (CSF) culture and polymerase chain reaction (PCR). In seventeen children (34.7%) data on the glucose ratio was missing, in 22 children (44.9%) the white blood cell count was unknown. PCR was conducted in 39 children (79.6%). The diagnostic criteria are shown in table 2.

Table 2 – Diagnostic Criteria for the Identification of Viral and Bacterial Etiologies of Non-Traumatic Coma

Viral	Confirmed bacterial meningitis	Bacterial meningitis medium possibility	Bacterial meningitis low possibility
• Virus found in PCR	• Bacteria identified in CSF	• Fever (>38 degrees Celsius) • Glucose ratio < 0.67 • White blood cell count > 5 mm^3	• Fever (>38 degrees Celsius) And one of the following: • Glucose ratio < 0.67 • White blood cell count > 5 mm^3 • Positive blood culture

CSF: Cerebrospinal fluid.
PCR: Polymerase chain reaction.

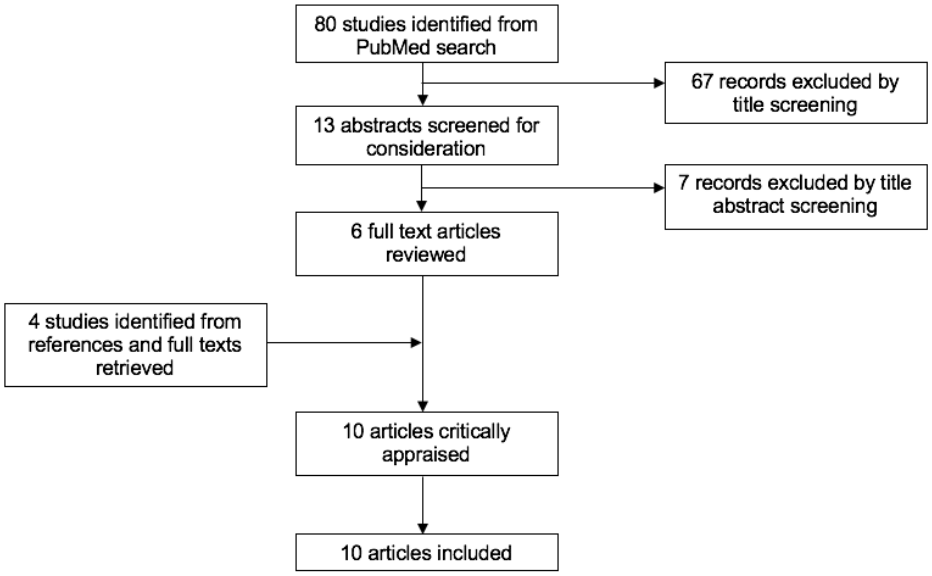
A secondary analysis consisted of the analysis of the outcomes at discharge for the five different malaria groups. There was no missing data. Three outcomes were possible: (1) died, (2) survived with neurologic sequelae or (3) survived.

RESULTS

PUBMED SEARCH

The PubMed search resulted in eighty articles from which thirteen abstracts were reviewed. Finally seven articles were identified for inclusion. An additional three studies were included after examining the references of the articles. The flowchart of the collection of the publications is shown in Figure 1.

FIGURE 1 – FLOWCHART OF STUDY COLLECTION



CRITICAL APPRAISAL

The different studies that were retrieved were analyzed on the assessment criteria shown in table 3. The majority of the studies had a clearly defined aim, and inclusion and exclusion criteria. Statistical analysis was appropriate in almost all records. Follow-up was in all of the records poorly described, along with the description of confounding factors. Since the outcome at discharge was a secondary outcome in this thesis, the poorly described follow-up in the articles did not fundamentally affect the results. Beyond that, the overall appraisal of the articles retrieved was sufficient.

Table 3 – Critical Appraisal of Quality for the Selected Studies										
Assessment criteria	**Berkley et al.**	**Gwer et al. (2015)**	**Ibekwe et al.**	**Laman et al.**	**Macpherson et al. (2007)**	**Macpherson et al. (2013)**	**Schubart et al.**	**Serem et al.**	**Taylor et al.**	**White et al.**
Was the aim of the study clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were inclusion and exclusion criteria clearly defined?	Y	Y	N	Y	Y	Y	N	Y	Y	Y
Was the study period carried out over a sufficient time period for outcomes to occur?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was follow up complete, and if not reasons to loss to follow up described?	U	U	U	U	U	U	U	U	N/A	N/A
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	U	Y	U	Y
Were confounding factors described and strategies to deal with them stated?	N	Y	N	N	N	N	Y	N	N	N
Played the funding source a role in the study?	U	N	U	N	N	N	N	N	N	U
Overall appraisal: Y/N?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y = Yes, N = No, U = Unclear, N/A = Not applicable

LITERATURE DATA EXTRACTION

Table 4 shows an overview of the etiological distribution of the different etiologies of non-traumatic coma and seizures.

Table 4 – Etiological Distribution of Malaria, Viruses and Bacteria in children with Non-traumatic Coma or Seizures							
Author	**Year**	**Sample size**	**Country**	**Malaria**	**Viral**	**Bacterial**	**Unknown origin**
Gwer et al.	2015	665	Kenya	392 (59%)	-	27 (4%) (ABM)	239 (36%)
Schubart et al.	2006	96	Kenya	49 (51%)	12% (HSV-1)	-	47 (49%)
Macpherson et al.	2007	789	Malawi	487 (62%)	10 (1,3%)	-	-
Macpherson et al.	2013	513	Malawi	163 (32%)	26% (adenovirus (42), mumps (29), HHV-6 (16), rabies (14), CMV (12), HSV-1 (8) and enterovirus (8))	-	-
Berkley et al.	1998	555	Kenya	297 (54%)	-	14 (2,5%) (ABM)	28 (5%)
Serem et al.	2015	2742	Kenya	899 (33%)	?	?	467 (17%)
Laman et al.	2014	554	Papua New Guinean	-	22 (4%) (SSPE)	47 (8,5%) (meningitis)	-
White et al.	2009	64	Malawi	35 (55%)	-	9 (14%) (ABM, sepsis)	20 (31,3%)
Ibekwe et al.	2018	40	Nigeria	19 (47,4%)	-	11 (27,5%) (ABM, septicemia)	10 (25%)
Taylor et al.	2004	42	Malawi	31 (74%)	-	6 (14%) (ABM (4), sepsis (2))	-

ABM = Acute Bacterial Meningitis; HSV-1 = Herpes Simplex Virus type 1; HSV-2 = Herpes Simplex Virus type 2; HHV-6 = Human Herpes Virus 6; CMV = Cytomegalovirus; SSPE = Subacute Sclerosing Pan Encephalitis.

-: no data.

?: cause is known, but unknown whether it is viral or bacterial.

The baseline characteristics, symptoms and outcomes are shown in table 5. The median age of the children was 47 months. A median weight of 33 kg was found. More than half of the children was of the male sex (59%). A substantial proportion of the children presented with fever (96%). 33 children had convulsions of the 47 (data on two children was missing), thus 70% of the children had convulsions. The greatest proportion of the children was referred from the Health Centre to the Queen Elizabeth hospital, followed by referral from home (14.3%), other places (4.1%) and the District Hospital (2.0%). 100% of the children had a BCS $\leq$ 2 and 23.3% of the children had a status epilepticus. The children were grouped into coma and status epilepticus, but could also be placed in both groups. HIV status was established for 42 children with a HIV rapid test, of whom two were HIV positive, forty were HIV negative and of seven children there was no data. 43 children survived (69.4%) and three with neurologic sequelae (6.1%), and three died (6.1%).

Table 5 – Baseline Characteristics, Symptoms and Outcomes in Children with Non-Traumatic Coma

Basic characteristics, symptoms and outcomes	**All (n = 49)**
Male sex	29 (59%)
Age (months)	47 (30-74)
Weight (kg)	13 (12-16.75)
Convulsions	33/47* (70%)
Fever	47 (96%)
BCS total	2 (1-2)
Referral - Home - Health Centre - District Hospital - Other	 7 (14.3%) 39 (79.6%) 1 (2.0%) 2 (4.1%)
Group** - Coma (BCS $\leq$ 2) - Status epilepticus	 49 (100%) 7/30* (23.3%)
HIV status - Positive - Negative - Not known	 2 (4.1%) 42 (49%) 7 (14.3%)
Outcome - Survived - Survived with neurologic sequelae - Died	 43 (69.4%) 3 (6.1%) 3 (6.1%)

**Data was missing, but still used for the analysis.*

***Patients could be placed into both groups.*
Data are n (%) or median (IQR).

The 49 children were classified into five groups, depending on the probability of cerebral malaria based on the before-mentioned algorithm. 31 children (63.3%) had a confirmed diagnosis of cerebral malaria. Three children (6.1%) had an high probability of cerebral malaria. A medium probability of cerebral malaria was found in ten children (20.4%). Three children had a low probability (6.1%). Two children (4.1%) had definitely not cerebral malaria.

To answer the third part of the aim of the thesis: to identify the potential bacterial and viral alternative etiologies in the 49 Malawian children with non-traumatic coma, the children were investigated in more detail on the probability of bacterial meningitis and viral causes. The results are shown in table 6. In thirteen children (26.5%) a medium or low probability of bacterial meningitis was found and in four children (8.2%) a possible viral cause. Patients could have a possible viral and bacterial cause at the same time. The majority of the possible bacterial meningitis and viral causes are found in the confirmed cerebral malaria group. The outcomes at discharge were analyzed in the different malaria groups, these results can also be found in table 6. One of the three patients that deceased had as PCR results rabies, which probably was the cause of death. Two patients with neurologic sequelae were found in patients with confirmed cerebral malaria, and one in a child with no cerebral malaria. The greatest proportion of the children who survived were found in the 'confirmed cerebral malaria' group.

Table 6 – Results of the Possible Viral and Bacterial Etiologies of Non-Traumatic Coma in Children and Outcomes at Discharge

	Confirmed cerebral malaria (n=31)	**High probability (n=3)**	**Medium probability (n=10)**	**Low probability (n=3)**	**No cerebral malaria (n=2)**
Confirmed bacterial meningitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Medium probability of bacterial meningitis	1 (3.2%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)
Low probability of bacterial meningitis	7 (22.6%)	1 (33.3%)	2 (20%)	0 (0%)	1 (50%)
Viral	2 (EBV and HHV-7) (6.45%)	0 (0%)	0 (0%)	1 (HHV-6) (33.3%)	1 (Rabies) (50%)
Died	1 (3.2%)	0 (0%)	0 (0%)	1 (33.3%)	1 (50%)

Neurologic sequelae	2 (6.4%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)
Survived	28 (90.3%)	3 (100%)	10 (100%)	2 (66.6%)	0 (0%)

EBV = Epstein-Barr Virus.
HHV-6 = Human Herpesvirus 6.
HHV-7 = Human Herpesvirus 7.
Data are n (%).
Patients could have bacteria and viruses at the same time.

DISCUSSION

Non-traumatic coma is a significant problem in children in low-income countries like Malawi. The outcomes of experiencing non-traumatic coma in children are serious, like neurologic sequalae and even death. Cerebral malaria was often thought to be the most common cause of NTC, but over the past twenty years the prevalence of malaria has declined in some countries. During this time, it became clear that a great number of different etiologies could also be the possible cause of the non-traumatic coma. Beforehand this was not noticed, probably because a lot of over-diagnosis of cerebral malaria had happened, masking the actual etiology. Which in fact is still happening in some regions. Partly this was caused by the difficulty of diagnosing cerebral malaria. The diagnosis of cerebral malaria is complicated because of limited diagnostic resources, the high prevalence of asymptomatic parasitemia and the similarity between the different etiologies. As a consequence, a lot of the causes of non-traumatic coma in low-income countries still have to be un- or discovered and investigated.

In this thesis the problem of malaria over-diagnosis was highlighted by analyzing a cohort of 49 Malawian children with non-traumatic coma in 2015 and it was attempted to identify the probability of a malarial infection and the possible alternative infectious causes. To gain knowledge on the range of etiologies causing non-traumatic coma and to understand the pathophysiology of cerebral malaria, a literature review was performed. Based on the included articles, a diagnostic algorithm was developed, to determine the likelihood of cerebral malaria as the cause of the non-traumatic coma. Next, alternative bacterial and viral etiologies were identified, since these are the most common causes besides malaria. Finally the data was compared to datasets with the records retrieved from the literature review.

In the dataset, the greatest proportion of the children had a confirmed cerebral malaria (63.3%). This percentage is higher compared to the percentage identified in the analyzed records (32-59%). This difference is possibly due to the exclusion of children with a high probability of bacterial meningitis, based on the clinical presentation, in the dataset, which results in a higher percentage of children with malaria. 32.7% of the children had a high, medium or low probability of cerebral malaria, their final diagnosis is therefore unconvincing. These numbers are higher compared to the numbers found in the study from Kenya (J. A. Berkley, 1999) where 13% of all children had an unclear diagnosis. On the other hand, they are lower compared with the publication on viral pathogens from Papua New Guinea (Moses Laman, 2014) were an unclear diagnosis was also found in 59% of the children. In these children with a possible CNS infection an etiologic agent was not determined. This can be due to different definitions of ‘unclear’ diagnosis. The majority of the medium and low probability of

bacterial etiologies was found in the 'confirmed cerebral malaria' group, which was unsuspected. In 3.2% of the children with confirmed cerebral malaria there was a medium probability that they had a bacterial meningitis, and in 22.6% there was a low probability that they had bacterial meningitis. These data correspond with the results in the retrospective analysis from Kenya (J. A. Berkley, 1999), where 13% of the children had a asexual malaria parasitemia and a possible meningitis. The presentation of bacterial meningitis is very similar to the presentation of malaria.

The 4 viruses identified in the 49 children in Malawi were EBV, HHV-6, HHV-7 and rabies. The study from Papua New Guinea (Moses Laman, 2014) established also HHV-6 and HHV-7, and dengue and enterovirus as causes for central nervous system infections. A short report from Kenya (Christian D. Schubart, 2006) identified HSV-1 in 12% of the children with encephalitis. HSV-1 was included in the PCR panel, but not identified in the dataset.
The viruses found in a cohort study in Malawi (Macpherson Mallewa P. V., 2013) are comparable with the viruses identified in the dataset. The viruses that were found most frequently in the Malawi cohort study were adenovirus, mumps virus, HHV-6 and rabies. They also identified HHV-6 and rabies. Remarkably, in this study, the most common virus that was detected was adenovirus, while in the dataset no adenoviruses were identified. The reason for this could be an over-diagnosis of adenovirus due to contamination, since they conducted a conventional PCR to detect adenovirus. Conventional PCRs are prone to contamination, and ideally a quantitative PCR (as performed in the current Malawian cohort study) is performed to decrease the change of a false-positive PCR result (Eunkyung Song, 2017). An alternative explanation could be since the data from the Malawian cohort study are from 2002 to 2004, the prevalence of adenoviruses was possibly higher compared with 2015.
The authors from the Malawian cohort study also investigated in their study population rabies as a cause of fatal CNS infection (Macpherson Mallewa A. R., January 2007). They found that 10.5% of the fatal CNS infections was due to rabies. In the dataset rabies was detected in one child with no cerebral malaria. Rabies was not detected in the children with confirmed or probable cerebral malaria. While in the rabies Malawi study (Macpherson Mallewa A. R., January 2007) it was identified that 11.5% of the children with fatal cerebral malaria actually died of rabies. The low number of rabies in the dataset is probably an underestimation, since there is an increase in rabies cases in children in Malawi (Sarita Depani, 2012). This underestimation could be due to the death of the children with rabies before being able to include them in the cohort.

Two of the four viruses (EBV and HHV-7) identified were found in patients who also had confirmed cerebral malaria. The overlap between the viral and malarial diagnostic groups is

also described in some records. The Papua New Guinean study (Moses Laman, 2014) found that nineteen of the 155 identified pathogens determined in children with possible CNS infection could be a possible viral and malarial infection, therefore these children could be diagnosed with more possible infections. A study from Kenya (Christian D. Schubart, 2006) found that in children with cerebral malaria, 9% had also a possible HSV-1. The Malawi cohort study identified that in one third of the children with cerebral malaria also viral infections were detected (Macpherson Mallewa P. V., 2013).

In the dataset a low total mortality rate (6.1%) and low total number of children with neurologic sequelae (6.1%) was established. This is low, compared to the mortality rate of 18% and 11% with neurologic sequelae found by the Malawian cohort study (Macpherson Mallewa P. V., 2013). The difference in mortality and neurologic sequelae numbers could be due to improved treatment for malaria (Don P. Mathanga, 2012 Mar). In the cohort of 49 Malawian children, 3.2% of the children with confirmed cerebral malaria died. Significantly lower compared to the case death of 16% in comatose children for malaria in the retrospective analysis from Kenya (Samson Gwer N. T., 2012), and to the mortality rate of 20% due to malaria reported by another study from Kenya (George K. Serem, 2015). The Malawian cohort study (Macpherson Mallewa P. V., 2013) identified that 32% of the children died with malaria parasitemia in the blood. These different numbers could be also due to improved treatment.

This thesis also has some limitations. The analysis of the literature can be biased because of a few reasons. The majority of the records are written by the same investigators: Malcolm Molyneux in four, Charles RJC Newton and Terrie E Taylor in three, Samson Gwer and Macpherson Mallewa in two of the ten records. As a consequence, the interpretation of the data is very similar, therefore other possible interpretations on results are lacking. The ten records that were retrieved from the PubMed search were first critically appraised before compared with each other. But the extent to which these are comparable is negotiable. Not all studies used the same definitions for coma and convulsions, nor the same definitions for the malarial, viral and bacterial etiologies. For example, to define ‘coma’ the retrospective analysis from Kenya (Samson Gwer N. T., 2012) used a BCS < 2, while the Malawian cohort study (Macpherson Mallewa P. V., 2013) used a BCS $\leq$ 4 and another Kenyan retrospective analysis (J. A. Berkley, 1999) a BCS < 5. The short report from Kenya (Christian D. Schubart, 2006) used the WHO definition for cerebral malaria, while the Kenyan retrospective analysis (J. A. Berkley, 1999) and the Malawian cohort study (Macpherson Mallewa P. V., 2013) diagnosed children with cerebral malaria if they found asexual forms of *Plasmodium falciparum* parasites in peripheral blood combined with coma that is not due to an alternative cause. This can lead to skewed results. The data retrieved from the articles is not always from after the malaria-

decline, which can result in a higher rate of malaria as a cause of non-traumatic coma. Only a few of the retrieved studies were conducted in Malawi. Publications from different countries that were malaria-endemic, low-income or in Africa were stated as comparable and therefore included. It is negotiable whether these countries really are comparable.
The results from the dataset also have some limitations. The children were classified into five groups for the probability of cerebral malaria. It is negotiable if the organization of these groups is accurate. It was chosen that the likelihood of cerebral malaria increased with respectively a positive RDT, positive slide and a positive retinopathy. This assumption was made based on pathophysiological data about cerebral malaria retrieved from my literature search, but it is questionable to what extent this data is true.
Furthermore, the results from the malaria tests carried out in the children can be distorted because a lot of the children received anti-malaria drugs before presenting to the hospital, which can skew the results in the thesis. Sometimes data of the malaria testing was missing, but these children still were included, which can also distort the results. This also applies to the results on bacterial meningitis. Moreover, the children with a high probability of bacterial meningitis were excluded, which has major consequences on the prevalence numbers of bacterial meningitis. The organization of the children in the groups for bacterial meningitis is negotiable. To classify the children in these groups, results on just a few tests were used. Results from more tests could have made the classification of the children in these groups more careful, like CSF results of the opening pressure, the cell differential and protein number. Children sometimes received antibiotics before testing on bacterial meningitis, which results in a negative blood culture, and a lower probability of bacterial meningitis. The data on bacterial meningitis can be an underestimation. Furthermore, a PCR was performed in only 39 of the 49 children (79.6%), but still all the children were considered for the analysis. The lack of data can bias the results. A more precise classification could have been established if more results on tests would have been taken into account, except for only using a positive PCR. For example the results of a lumbar puncture on the following test: the opening pressure, the white blood cell count, the cell differential, the protein number and the CSF-to-serum glucose ratio.

The strengths of this thesis are the following. The data are collected relatively recently, from after the malaria-decline, which makes the results of the thesis generalizable for the current situation in Malawi. For the (probable) diagnosis of cerebral malaria, retinopathy was taken into account which has not been done a lot before. All of the results are easy to interpret due to the clear display of the results in the tables. The records retrieved for the analysis were critically appraised, which made sure that only articles of good quality were used.

A few implications of practice are the following. Clinicians need to be made aware that a lot of children are over-diagnosed with cerebral malaria. To reduce the number of over-diagnosing these clinicians need to learn about the different other possible etiologies. The clinical presentation of cerebral malaria is very similar to the other bacterial or viral causes of non-traumatic coma. Therefore, clinicians need to learn that the finding of a typical clinical presentation of cerebral malaria is not sufficient for the diagnosis cerebral malaria.

This thesis aimed to identify the etiology of infectious non-traumatic coma in 49 Malawian children. This brings us one step closer in combating non-traumatic coma in children. But still, a lot of further research is needed. Only infectious causes are highlighted in this thesis, but non-communicable diseases can also cause non-traumatic coma which need to be investigated. Viruses as cause of non-traumatic coma need to be further investigated since there is a paucity in knowledge on these causes. Only a few records have reported on viral causes (Macpherson Mallewa P. V., 2013), (Moses Laman, 2014), (Christian D. Schubart, 2006). The focus of this thesis is on the etiology, but what is also important to investigate is the pathophysiology, risk factors, outcome indicators and outcomes for the different etiologies. A great overlap is found in children between cerebral malaria and viral and bacterial causes. It is important to create a diagnosing tool for cerebral malaria that excludes these similar causes and takes new developments on the diagnosing of cerebral malaria into account, like retinopathy. This will reduce the number of over-diagnosing of cerebral malaria.
Collecting data on these matters will help to find the appropriate interventions that would significantly reduce the incidence of non-traumatic coma.

CONCLUSION

This thesis indicates that cerebral malaria still is one of the most common causes of non-traumatic coma. But bacterial and viral infections can also possibly cause non-traumatic coma. Differentiating between bacterial, viral or malarial causes of non-traumatic coma based on clinical data and basic laboratory results, remains a challenge. Further research on and improved control of malaria and other infections should help to develop interventions to combat non-traumatic coma in children.

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Table 1 – Diagnostic Criteria for the Probability of Cerebral Malaria for Children with a BCS ≤ 2				
Confirmed	**High probability**	**Medium probability**	**Low probability**	**No Cerebral Malaria**
• Retinopathy positive • Slide positive at A&E of Admission	• Retinopathy positive • Slide or RDT unknown or negative at A&E or Admission	• Retinopathy negative • Slide positive at A&E or Admission	• Retinopathy negative • Only RDT positive at previous RDT, A&E or Admission	• Retinopathy negative • RDT and slide negative at previous RDT, A&E and Admission
Retinopathy: a positive test means that retinopathy is present. *Slide: thick peripheral blood smear.* *RDT: rapid diagnostic test.* *A&E: Accident & Emergency Department.*				

Table 2 – Diagnostic Criteria for the Identification of Viral and Bacterial Etiologies of Non-Traumatic Coma			
Viral	**Confirmed bacterial meningitis**	**Bacterial meningitis medium possibility**	**Bacterial meningitis low possibility**
• Virus found in PCR	• Bacteria identified in CSF	• Fever (>38 degrees Celsius) • Glucose ratio < 0.67 • White blood cell count > 5 mm^3	• Fever (>38 degrees Celsius) And one of the following: • Glucose ratio < 0.67 • White blood cell count > 5 mm^3 • Positive blood culture
CSF: Cerebrospinal fluid. *PCR: Polymerase chain reaction.*			

Table 3 – Critical Appraisal of Quality for the Selected Studies										
Assessment criteria	**Berkley et al.**	**Gwer et al. (2015)**	**Ibekwe et al.**	**Laman et al.**	**Macpherson et al. (2007)**	**Macpherson et al. (2013)**	**Schubart et al.**	**Serem et al.**	**Taylor et al.**	**White et al.**
Was the aim of the study clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were inclusion and exclusion criteria clearly defined?	Y	Y	N	Y	Y	Y	N	Y	Y	Y
Was the study period carried out over a sufficient time period for outcomes to occur?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was follow up complete, and if not reasons to loss to follow up described?	U	U	U	U	U	U	U	U	N/A	N/A
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	U	Y	U	Y
Were confounding factors described and strategies to deal with them stated?	N	Y	N	N	N	N	Y	N	N	N
Played the funding source a role in the study?	U	N	U	N	N	N	N	N	N	U
Overall appraisal: Y/N?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y = Yes, N = No, U = Unclear, N/A = Not applicable										

Table 4 – Etiological Distribution of Malaria, Viruses and Bacteria in children with Non-traumatic Coma or Seizures							
Author	**Year**	**Sample size**	**Country**	**Malaria**	**Viral**	**Bacterial**	**Unknown origin**
Gwer et al.	2015	665	Kenya	392 (59%)	-	27 (4%) (ABM)	239 (36%)
Schubart et al.	2006	96	Kenya	49 (51%)	12% (HSV-1)	-	47 (49%)
Macpherson et al.	2007	789	Malawi	487 (62%)	10 (1,3%)	-	-
Macpherson et al.	2013	513	Malawi	163 (32%)	26% (adenovirus (42), mumps (29), HHV-6 (16), rabies (14), CMV (12), HSV-1 (8) and enterovirus (8))	-	-
Berkley et al.	1998	555	Kenya	297 (54%)	-	14 (2,5%) (ABM)	28 (5%)
Serem et al.	2015	2742	Kenya	899 (33%)	?	?	467 (17%)
Laman et al.	2014	554	Papua New Guinean	-	22 (4%) (SSPE)	47 (8,5%) (meningitis)	-
White et al.	2009	64	Malawi	35 (55%)	-	9 (14%) (ABM, sepsis)	20 (31,3%)
Ibekwe et al.	2018	40	Nigeria	19 (47,4%)	-	11 (27,5%) (ABM, septicemia)	10 (25%)
Taylor et al.	2004	42	Malawi	31 (74%)	-	6 (14%) (ABM (4), sepsis (2))	-

ABM = Acute Bacterial Meningitis; HSV-1 = Herpes Simplex Virus type 1; HSV-2 = Herpes Simplex Virus type 2; HHV-6 = Human Herpes Virus 6; CMV = Cytomegalovirus; SSPE = Subacute Sclerosing Pan Encephalitis.

-: no data.

?: cause is known, but unknown whether it is viral or bacterial.

Table 5 – Baseline Characteristics, Symptoms and Outcomes in Children with Non-Traumatic Coma	
Basic characteristics, symptoms and outcomes	**All (n = 49)**
Male sex	29 (59%)
Age (months)	47 (30-74)
Weight (kg)	13 (12-16.75)
Convulsions	33/47* (70%)
Fever	47 (96%)
BCS total	2 (1-2)
Referral - Home - Health Centre - District Hospital - Other	 7 (14.3%) 39 (79.6%) 1 (2.0%) 2 (4.1%)
Group** - Coma (BCS ≤ 2) - Status epilepticus	 49 (100%) 7/30* (23.3%)
HIV status - Positive - Negative - Not known	 2 (4.1%) 42 (49%) 7 (14.3%)
Outcome - Survived - Survived with neurologic sequelae - Died	 43 (69.4%) 3 (6.1%) 3 (6.1%)
**Data was missing, but still used for the analysis.* ***Patients could be placed into both groups.* *Data are n (%) or median (IQR).*	

Table 6 – Results of the Possible Viral and Bacterial Etiologies of Non-Traumatic Coma in Children and Outcomes at Discharge

	Confirmed cerebral malaria (n=31)	**High probability (n=3)**	**Medium probability (n=10)**	**Low probability (n=3)**	**No cerebral malaria (n=2)**
Confirmed bacterial meningitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Medium probability of bacterial meningitis	1 (3.2%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)
Low probability of bacterial meningitis	7 (22.6%)	1 (33.3%)	2 (20%)	0 (0%)	1 (50%)
Viral	2 (EBV and HHV-7) (6.45%)	0 (0%)	0 (0%)	1 (HHV-6) (33.3%)	1 (Rabies) (50%)
Died	1 (3.2%)	0 (0%)	0 (0%)	1 (33.3%)	1 (50%)
Neurologic sequelae	2 (6.4%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)
Survived	28 (90.3%)	3 (100%)	10 (100%)	2 (66.6%)	0 (0%)

EBV = Epstein-Barr Virus.
HHV-6 = Human Herpesvirus 6.
HHV-7 = Human Herpesvirus 7.
Data are n (%).
Patients could have bacteria and viruses at the same time.

FIGURE 1 – FLOWCHART OF STUDY COLLECTION