Incidence and Mortality of childhood Non-Traumatic Coma of Unknown Cause in Kilifi County between 2002 to 2018

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DECLARATION

I declare that this research report is my own work. It is being submitted for the degree of Master of Science in Epidemiology in the field of Biostatistics at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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10th June 2021

AGREEMENT BY CO-AUTHORS

Emily Odipo, student number 2103465 cleaned the data, performed data analysis, wrote the first draft and received critical comment from all co-authors. By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Research Report.

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DEDICATION

This Master's degree is dedicated to my dear husband David Barney who has offered unwavering support and encouragement throughout the whole purpose, my parents Mr. and Mrs. Odipo for the prayers and encouragement.

ABSTRACT

Background: Acute non-traumatic coma (aNTC) is a neurological emergency often seen in paediatric presentation in sub-Saharan Africa and is associated with high morbidity and mortality. Malaria and invasive bacteria were often linked to the etiology of aNTC but the etiology of a significant proportion of children admitted with aNTC remains unknown. These children with coma of unknown cause (CUC) are at a higher risk of death and long-term sequelae compared to those with known cause. Despite this, up-to-date population-based data on the incidence, etiology, severity, and outcome of CUC in children is lacking especially in Low and middle income (LMIC) settings. Such data are a prerequisite for informed provision of healthcare resources for this patient group. The objective of this study was to determine the incidence, mortality, and temporal trends of childhood admissions with CUC in Kilifi County Hospital located on the Kenyan Coast.

Methods: We reviewed Kilifi County Hospital coma admission records for children aged 2 months to 13 years between 2002 to 2018 (Blantyre Coma Score<3). Patients with CUC were identified among the non-traumatic coma cases after excluding those defined as having cerebral malaria (CM) and meningitis. The incidence for CUC was restricted to within the Kilifi Health and Demographic Surveillance (KHDS) geographical area residents. Trend of acute non-traumatic coma (aNTC) admissions was explored and a logistic model was fitted to determine the risk factors associated with CUC mortality among children.

Results: During the study period, there were 3590 (6.5%) children admitted with aNTC. Of these, 74 (2%), 1507 (42%) and 1496 (41%) were due to Meningitis, CM and CUC respectively. Additionally, 540 (15%) were ungrouped due to missing data. The average Incidence of CUC was 36 per 100,000-person years. Age specific analysis showed that younger children had a higher incidence rate of CUC as compared to older children. During the study period 325 CUC cases died with the risk of death showing inverse relation with age: <1yr (44%), 1-2yrs (30%), 3-5yrs (13%) and 6-13yrs (13%). Trend analysis showed significant decline in admissions with CM and meningitis and a significant rise in CUC during 2002-2018 - a period of declining malaria and introduction of conjugate vaccines against *Hemophilus influenza* and *Streptococcus pneumoniae*.

In multivariate analysis, MUAC, hypoxia, lymphadenopathy and irregular respiration were found to be risk factors associated with CUC mortality within the CUC group.

Conclusion: With the decline in malaria transmission and introduction of vaccines against *Haemophilus influenza* and Pneumococcus, there has been a decline in hospital admission due to CM and Meningitis. These declines have been accompanied by a significant increase in admissions due to CUC. Therefore, understanding the etiology of CUC is critical in improving diagnosis and treatment, and in developing preventive measures which can ultimately reduce incidence and improve hospital outcome.

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- ABM – Acute bacterial meningitis
- aNTC - Acute non-traumatic coma
- CM – Cerebral malaria
- CNS – Central nervous system
- AS- Acute Seizures
- PCV – Pneumococcal conjugate vaccine
- CUC – Coma of unknown cause
- KCH – Kilifi County Hospital
- KEMRI – Kenya Medical Research Institute
- BCS – Blantyre coma score
- KHDSS – Kilifi Health and Demographic Surveillance System
- MUAC – Mid upper arm circumference
- SARIMA – Seasonal autoregressive integrated moving average
- ACDC – Africa Centre for Disease Control and Prevention
- GCS- Glasgow Coma Scale
- TBI- Traumatic Brain Injury
- MCS- Minimally Conscious State
- EEG- Electroencephalogram
- RDT- Rapid Diagnostic Test
- CSF – Cerebrospinal fluid
- LMIC – Low and middle-income countries

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Introduction

Acute non-traumatic coma (aNTC) is a neurological emergency associated with high morbidity and mortality(1) . Malaria and bacterial infection, metabolic derangements, and poisoning are some of the common causes of aNTC(1, 2). However, a proportion of those admitted with aNTC have no known cause identified using the routine laboratory investigation, although the clinical symptoms suggest infection. This subgroup of aNTC is commonly referred to as coma of unknown cause (CUC)(1, 2). Importantly, many children with CUC are at a higher risk of death and neurological impairment(3, 4) probably because the unknown cause is not objectively targeted for treatment. Population based data on the incidence, aetiology, severity, and outcome of CUC in children is lacking especially in LMIC settings(5). Such data are a prerequisite for informed provision of healthcare resources for this high-risk group with including neurological disability.

Infectious diseases resulting to coma account for between 3-15% of emergency hospital admissions in developing countries(1). However, the etiology of most aNTC admissions in sub-Saharan remain unknown although infections are highly suspected. In sub-Saharan Africa, aNTC is often attributed to cerebral malaria (CM) or acute bacterial meningitis (ABM) (1, 2, 6, 7). Malaria has declined in most areas and the introduction of bacteria vaccines has resulted in a reduction in meningitis cases(8). Approximately 33% of childhood aNTC admissions are fatal while a significant occurrence of neurocognitive sequelae including impaired attention, memory loss and impaired social functioning is reported among survivors(9, 10).In Kilifi county hospital (KCH), located along the Kenyan coast, aNTC was mostly linked to ABM and CM though the underlying cause of coma for a high proportion of paediatric admission remains unknown (5). Children admitted with CUC face a high risk of death and neurological impairment since their treatment is not based on diagnosis (11). Previously, Gwer and colleagues showed that the incidence of childhood coma in KCH reduced from 93/100 000 children to 44/100 000 children in 2004 and 2009 respectively. This study aimed to determine the incidence, mortality, and temporal trends of childhood admissions with CUC in KCH located on the Kenyan Coast over a longer period (2002-2018). We reviewed hospital admissions records at KCH over the last 16 years (2002-2018) among children aged 2 months to 13 years.

Problem statement

Many children admitted to hospital with CUC especially in LMICs are at a higher risk of death and neurological impairment(5). While diagnosis remains a major challenge due to limited resources, there is lack of data on incidence and outcome of such admissions. Literature on paediatric NTC in general is limited while that specific for CUC is quite scanty especially in sub Saharan Africa. Gwer and colleagues identified and reviewed 14 studies on the aetiology of childhood acute NTC in resource-poor countries(12). Cerebral malaria (CM) was the leading cause of childhood coma in the seven studies that were conducted in Africa while ABM was the second most cause of coma(12). Further, review of KCH admission data between 2004-2009 by Gwer et al revealed that admissions due to CUC were on the rise. However, up-to-date data on the incidence of CUC is lacking as several interventions such as Pneumoccal vaccine were introduced in the last 10 years (5).

There is limited data on incidence, causes and outcome of aNTC in LMIC which is vital to help improve outcome and to organize meaningful clinical management of NTC. Such data can also act as a basis for improving healthcare resources to this high-risk group. The outcome of this study will form the basis of research aimed at identifying the aetiology of CUC and ultimately improve the management of this condition.

Justification of the study

CUC is an important emergency presentation in several referral hospitals in developing countries. The incidence and outcome of CUC has not been systematically documented and remains unknown in many settings. Indeed, only very few studies have been conducted towards understanding the incidence and trend in CUC admissions (5). Hospitalization with CUC presents a care and management challenge for many hospitals with limited facilities and since the aetiology remains unknown. Children hospitalized with CUC have varied outcomes such as death or varying degree of neurological disability. It is therefore important to review existing KCH admission data and provide incidence of CUC.

Between 2004 and 2009, the proportion of children admitted at KCH with CUC was shown to have increased which coincided with a fall in malaria and ABM cases (5). The introduction of the ten-valent pneumococcal conjugate vaccine (PCV10) in January 2011 in Kenya accompanied by a catch-up campaign in Kilifi County for children aged younger than 5 years (8) reduced the burden of hospital admissions for childhood pneumonia in Kilifi. However, there was an insignificant reduction in the proportion of those diagnosed with pneumococcal meningitis when the pre-vaccine era (1999–2010) was compared with post-vaccine era (2012–16) among children below 14 years (13) . There was also a decline in malaria admissions from 18·43 per 1000 children to 3·42 in 2003 and 2007 respectively, coupled with a decrease in malaria mortality (14). Recently, Njuguna and colleagues showed that between 2004–2008, and 2009–2016, KCH admitted averages of 310 and 174 cases of severe malaria per year including averages of 14 and 12 malaria-associated deaths per year, respectively. Taking into account such changes, it is likely that the annual incidence rates and etiology of CUC have changed. However, no formal analysis has been carried out and the current burden of CUC remains unknown. It is therefore important to review existing data and provide up-to-date incidence of CUC.

This study sought to determine the incidence and mortality of CUC among childhood admissions of aNTC in Kilifi County Hospital. The study utilized hospital records to determine the trends and proportion of CUC between 2002-2018 among children aged 2 months to 13 years. The annual incidence of admissions and death associated with CUC was restricted to the KHDS geographical area within Kilifi County.

Literature Review

Epidemiology of non-traumatic coma

Global outlook

Globally, few studies have been carried out on the incidence, aetiology, and outcomes of hospital admissions of aNTC. Wong and colleagues reported an incidence of 30.8 per 100,000 children below sixteen years per year in a study carried out in the United Kingdom between July 1994 and December 1995 (15). They also observed that the age specific incidence was especially high during the 1st year of life (160/100,000 children per year) compared to ages 2 to 16 years where each year had less than 50/100,00 children per year (15). Presentations specific to CNS were frequent as age increased. Among the infants, infection was the most common aetiology though none was identified in 14% of the infants. Aetiology specific mortality rates ranged from 3% to 84% with an overall series mortality at 46% from an approximate 1 year follow-up (16). Sofia et al followed up 116 post-natal children in Malaysia with NTC admitted over an 8 month period (17). Among these cases, eighty (69%) were due to infection, 13% to toxic metabolic causes, 5% to hypoxic ischaemic insults, 3.5% had intracranial haemorrhage, 7.8% were due to miscellaneous causes and in 1.7% of the cause was unknown. Of the 116 children, 33.6%, died while 27.5% developed permanent neurological deficit (17). Children aged between 1 month and 12 years presenting to hospital with febrile encephalopathy were studied prospectively taking a complete history, examination and laboratory investigations in Papua New Guinea (2). A definite pathogen was identifiable for 37% out of 149 children with diagnoses including hepatic encephalopathy, bacterial meningitis in, tuberculous meningitis, probable tuberculous meningitis, malaria and cryptococcal meningitis. Of the children followed, 41 (28%) had an adverse outcome where 13 (8.9%) died while 28 (19.2%) had severe neurological sequelae.

Fosberg et al, looked at the prognosis in non-traumatic coma cases in Sweden and observed eight different coma etiologies in 865 patients which were poisoning 38%, stroke 24.6%, epilepsy 13.1%, circulatory failure 6.9%, infection 6.5%, metabolic disorder 5.1%, respiratory insufficiency 3.8%, and intracranial malignancy 2%. The death rate was 26.5%, with a combined two year mortality rate of 43% (18). The study showed that the prognosis in non-traumatic coma cases is of great concern and greatly relies on etiology of the coma and extent of consciousness during admission.

In Asia, Gupta et al carried out an observational study in India, following 90 children aged between 1 month and 12 years with Acute Febrile Encephalopathy admitted in Paediatric intensive care unit (ICU). All children exhibited altered sensorium, about two thirds had seizures and 47.8% having a Glasgow Coma Score (GCS) <8. Aetiology remained elusive in about 40% of the cases, and viral infections were the most common among the ones with an identifiable cause (19). A variety of outcomes including shock, disseminated intravascular coagulopathy, and respiratory failure and mortality of 40% was observed. The risk factors associated with mortality were GCS < 8, the presence of raised intracranial pressure, shock, and respiratory failure(19).A small cross-sectional study in a referral hospital in Karachi, Pakistan among 100 paediatric patients below 14 years diagnosed with aNTC observed a mortality of 35%. Among the survivors (n=65), 41% exhibited disability(20). Infections (n=23, 79%) were attributed to be the major cause for mortality(20). A similar study carried out in India concluded that CNS infections including bacterial meningitis, encephalitis and tubercular meningitis were the common cause of aNTC in childhood at 60% with clinical signs as good indicators of the outcome. From the 65 children who survived, 16.9% were normal, 21.5% had mild disability, 32.3% had moderate disability and 21.5% were severely disabled and dependent (21).

In Saudi Arabia, a study looking at the etiology, incidence, and outcome in traumatic and NTC pediatric admissions for children aged 28 days to 12 years identified 43(47%) patients with non-traumatic coma out of 91 patients with coma, which was 5% of the overall admissions during the period. Of the NTC patients, 26 (61%) died(22). Other outcomes among the NTC cases included 7 impaired (alteration of tone, power or reflexes; cranial nerve dysfunction; ataxia; seizures; persistent vegetative states) and 10 intact (no change from premorbid functioning)(22). Taken together, these studies show that aNTC is still a major problem globally and more studies can be done to address the issues of diagnosis, management and prevention.

African situation

In Uganda, a prospective descriptive study of the aetiology of suspected CNS infections in 459 children aged two months to 12 years, with fever and at least one sign of CNS involvement in Mbarara Hospital, Uganda found that malaria *Plasmodium* (36%) and bacterial meningitis (13%) or bacterial sepsis (3%) were the most common diagnosis (23). Viral encephalitis was found in 27 (6%) children. No pathogen was isolated in 207 (45%) children. Infection patterns varied by age and HIV status and 18% of the children died during hospitalisation, and 23 (5.0%) during follow-up for 6 months (23). Forty-one (14%) children had neurological sequelae at the last visit. The high mortality and high rate of neurological sequelae highlighted the need for effective diagnosis(23).

Africa has observed a long-term reduction in the prevalence of *Plasmodium falciparum* from 40% between 1900-1929 to 24% between 2010-2015, punctuated by intervals of decreasing or increasing transmission (24). A retrospective analysis aimed at determining the incidence, etiology and outcome of non-traumatic coma in children in Abakaliki, Nigeria, observed that majority were aged 1 to 5 years with 79.5% of them deeply comatose on admission. Common causes of the NTC were infections, mainly, pyogenic meningitis, septicemia and CM. Mortality among the cases was 32.5% (25).

A prospective cohort study in Malawi carried out among 513 childhood admissions for children between 2 months to 15 years with suspected non-bacterial CNS infections reported 94 (18%) deaths. There were 34 (21%) deaths among 163 children who had *P falciparum* parasitaemia (26). Viruses were found in the CNS of133 children (26%), with 43 (33%) deaths recorded in the category. Both parasitaemia and viral infection were detected in 45 (9%) of the 513 children, with 27 (35%) of 78 diagnosed clinically having CM (26). Double infected children were highly likely to have seizures than were those with parasitaemia alone, viral infection only, or neither ($p<0{\cdot}0001$). Death was recorded in 45 children with double infection, compared to single infection of viral, parasitaemia and neither at 26, 17 and 34 cases respectively ($p<0{\cdot}0001$). Children with viral CNS infection had a significantly higher deaths than did those without ($p=0{\cdot}001$) (26).

A systematic literature review of studies prior to May 16th 2014 yielded manuscripts from seven countries including Nigeria, Zambia and Tanzania and showed that the characteristic causes of NTC in patients aged 16yrs and above were stroke (54%), poisoning 39%, post-anoxic coma 42% and metabolic causes 29% (27). Infection was a noticeable cause in the African setting as seen in 51% of patients (27). Mortality rate due to aNTC from the literature search ranged from 25% to 87% with the highest deaths in stroke at 95% and post-anoxic coma at 89% and lowest for poisoning and epilepsy at 39% and 10% respectively (27). Overall, it is evident that little research on NTC has be done in sub-Saharan Africa. Data available is scanty and this compounds the need to do more on NTC in the African context.

Kenyan situation

In Kilifi County, at the Kenyan Coast, both hospital admissions for malaria and malaria associated deaths have significantly declined over the last three decades (13, 28) . Further, the incidence of bacterial meningitis has also declined especially after the introduction of *Haemophilus influenza* B conjugate and pneumococcal conjugate (PCV) vaccines (9, 24).

The decline in malaria transmission and bacterial infection has translated into a significant reduction in hospital admissions and mortality from coma as a result of malaria and ABM and a rise in the relative number of admissions and death due to coma of unknown cause (5). Importantly, children with CUC were shown to be at a higher risk of death and neurological impairment due to treatment that is not based on diagnosis. Gwer et al showed that the underlying cause of coma was undetermined in 36% of all KCH admissions of children between 9 months and 13 years who presented with acute coma (BCS <2) between 2004 and 2009 (5). While a proportion of such admissions may be due to neurotrophic viruses, metabolic disorders or poisons, bacterial infection cannot be excluded. In malaria endemic areas, CM is likely overestimated mainly due to misdiagnosis and comorbidity (29-31). Asymptomatic malaria parasitemia can be frequent in such areas and the presence of malaria parasites may be coincidental to another cause such as virus or bacteria (32-35). In practice, children exhibiting a positive rapid diagnostic test (RDT) or malaria slide and clinical signs are treated for malaria.

A prospective observational study was conducted by Gwer et al at the paediatric high dependency unit at KCH, where acute coma patients between 9 months-13 years were monitored by electroencephalogram (EEG). Three hundred and sixty- three seizures were observed in 34% of the children of which 66% were electrographic and 31% electro-clinical. The study observed that clinical observation was not able to detect that all seizures and initial EEG background amplitude are likely to predict the course of paediatric NTC (36).

Serem et al examined the effect of decline in malaria and the increasing burden of neonatal admissions on the incidence, causes and phenotypes of acute seizures admitted to Kilifi County Hospital between 2009 and 2013. They observed a general incidence of 312 per 100,000/year (95 % CI, 295–329) for acute seizures(AS): 116 per 100,000/year (95 % CI, 106–127) for complex seizures and 443 per 100,000 live births (95 % CI, 383–512) for neonatal seizures. They recorded an increase in incidence of seizures-attributable to malaria. Key causes of acute seizures were malaria and respiratory tract infections at 33% and 19% respectively while for neonatal seizures neonatal sepsis (51 %), hypoglycemia (41 %) and hypoxic-ischemic encephalopathy (21 %) were identified as the major causes. Death was observed in 6 % of the acute seizures (AS) (37) .

Similar to the rest of the African continent, very little has been done on NTC in Kenya. Apart from the work done by Gwer at the Kenyan coast, there is virtually no literature available for the rest of the country.

Purpose of the study

The study aimed at determining the incidence, mortality, and clinical risk factors associated with in hospital mortality among paediatric admissions of CUC in KCH, a major referral hospital along the Kenyan Coast. Gwer et al reported previously that the incidence of childhood aNTC declined from 93/100 000 children in 2004 to 44/100 000 children in 2009 in Kilifi County Hospital and that decline was mainly attributed to reduced malaria transmission. However, during the same period, there was an overall increase in annual CUC admissions of 272%(5). Mortality among encephalopathy of undetermined aetiology (33%) was twice that attributable to malaria (16%)

and comparable to meningitis (35%) but lower than that for culture proven bacterial meningitis (50%) (5). Due to the changing trends of infectious disease over time, a review of the incidence and risk of mortality associated with CUC is warranted. Consequently, the results will contribute to improving population-wide estimates, identification, care and control of CUC.

Research question

What is the proportion, incidence, mortality, and clinical risk factors associated with mortality among childhood admissions of CUC in Kilifi county Hospital, Kenya from 2002-2018?

Study objectives

Main Objective

The study aimed to investigate the proportion, incidence, and mortality among children presenting with CUC in Kilifi county between 2002 and 2018.

Specific objectives

1. To determine the incidence, causes and outcome of CUC among children admitted in KCH, Kenya between 2002 and 2018.
2. To determine the risk factors for mortality in children presenting with CUC in Kilifi County Hospital, Kenya between 2002 and 2018.
3. To describe the temporal trends of CUC in Kilifi county, Kenya between 2002 and 2018.

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CHAPTER 2: SUBMISSIBLE MANUSCRIPT

Incidence and Mortality of childhood Non-Traumatic Coma of Unknown Cause in Kilifi County between 2002 to 2018

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2. Kemri-Wellcome Trust

ABSTRACT

Background: Acute non-traumatic coma (aNTC) is a neurological emergency often seen in paediatric presentation in sub-Saharan Africa and is associated with high morbidity and mortality. Malaria and invasive bacteria are often linked to the etiology of aNTC but the etiology of a significant proportion of children admitted with aNTC remains unknown. These children with coma of unknown cause (CUC) are at a higher risk of death and long-term sequelae compared to those with known cause. Despite this, up-to-date population-based data on the incidence, etiology, severity, and outcome of CUC in children is lacking especially in Low and middle income (LMIC) settings. Such data are a prerequisite for informed provision of healthcare resources for this patient group. The objective of this study was to determine the incidence, mortality, and temporal trends of childhood admissions with CUC in Kilifi County Hospital located on the Kenyan Coast.

Methods: We reviewed Kilifi County Hospital coma admission records for children aged 2 months to 13 years between 2002 to 2018 (Blantyre Coma Score<3). Patients with CUC were identified among the non-traumatic coma cases after excluding those defined as having cerebral malaria (CM) and meningitis. The incidence for CUC was restricted to within the Kilifi Health and Demographic Surveillance (KHDS) geographical area residents. Trend of acute non-traumatic coma (aNTC) admissions was explored and a logistic model was fitted to determine the risk factors associated with CUC mortality among children.

Results: During the study period, there were 3590 (6.5%) children admitted with aNTC. Of these, 74 (2%), 1507 (42%) and 1496 (41%) were due to Meningitis, CM and CUC respectively. Additionally, 540 (15%) were ungrouped due to missing data. The average Incidence of CUC was 36 per 100,000-person years. Age specific analysis showed that younger children had a higher incidence rate of CUC as compared to older children. During the study period 325 CUC cases died with the risk of death showing inverse relation with age: <1yr (44%), 1-2yrs (30%), 3-5yrs (13%) and 6-13yrs (13%). Trend analysis showed significant decline in admissions with CM and BM and a significant rise in CUC during 2002-2018 - a period of declining malaria and introduction of conjugate vaccines against *Hemophilus influenza* and *Streptococcus pneumoniae*. In multivariate analysis, MUAC, hypoxia, lymphadenopathy and irregular respiration were found to be risk factors associated with CUC mortality within the CUC group.

Conclusion: With the decline in malaria transmission and introduction of vaccines against *Haemophilus influenza* and Pneumococcus, there has been a decline in hospital admission due to CM and Meningitis. These declines have been accompanied by a significant increase in admissions due to CUC. Therefore, understanding the etiology of CUC is critical in improving diagnosis and treatment, and in developing preventive measures which can ultimately reduce incidence and improve hospital outcome.

INTRODUCTION

Acute non-traumatic coma (aNTC) is a neurological emergency associated with high morbidity and mortality(1) . Malaria and bacterial infection, metabolic derangements, and poisoning are some of the common causes of aNTC(1, 2). However, a proportion of patients admitted with aNTC have no known cause identified using the routine laboratory investigation, although the clinical symptoms suggest infection. This subgroup of aNTC is commonly referred as coma of unknown cause (CUC)(1, 2). Importantly, many children with CUC are at a higher risk of death and neurological impairment(3, 4) probably because the unknown cause is not objectively targeted for treatment. Population based data on the incidence, aetiology, severity, and outcome of CUC in children is lacking especially in LMIC settings (5). Such data are a prerequisite for informed provision of healthcare resources for this high-risk group. However, there is lack of the etiology of most admissions of aNTC among sub-Saharan countries where infections are highly suspected. In areas where malaria is common, aNTC is often attributed to cerebral malaria (CM) and acute bacterial meningitis (ABM) (1, 2, 6, 7).

In Kilifi county hospital (KCH), located along the Kenyan coast, aNTC has mostly been linked to viral encephalitides, ABM and CM though the underlying cause of coma for a high proportion of paediatric admission remains unknown (5).

While diagnosis remains a major challenge due to limited resources, there is lack of data on incidence and outcome of such admissions. Literature on paediatric aNTC in general is limited while that specific for CUC is scanty especially in sub-Saharan Africa. Gwer and colleagues identified and reviewed 14 studies on the aetiology of childhood acute non-traumatic coma in resource-poor countries(12). CM was the leading cause of childhood coma in the seven studies that were conducted in Africa while ABM was the second most cause of coma (38). Further review of KCH admission data between 2004-2009 by Gwer et al revealed that admission due to CUC was on the rise but up-to-date data on the incidence of CUC is lacking even as several interventions such as Pneumococcal vaccine were introduced in 2010. This study sought to determine the incidence, outcome and clinical factors associated with poor outcomes for admissions of aNTC in KCH. This study used hospital records to determine the trends and incidence of non-traumatic coma admissions due to CUC between 2002-2018.

METHODS

Study Setting

This study was conducted at Kilifi County Hospital (KCH, formerly Kilifi District Hospital) located centrally within Kilifi County (KC) along the Kenyan Coast. The area is rural and semi-arid with subsistence farming, fishing and tourism as the main economic activities (39). Kilifi County is a malaria-endemic region whose pattern of transmission and clinical spectrum have been previously described (28). Overall, there has been a significant drop in malaria cases over the years. KC is served by KCH as a first-choice referral facility for hospital admissions. KCH is equipped with a 70-bed capacity paediatric ward backed by a 15-bed high dependency unit (HDU) used for admission of serious illnesses(28). The hospital receives approximately 5000 childhood admissions annually of which about 15% are severe and admitted in the HDU(28). The Kilifi Health and Demographic Surveillance System (KHDSS) is an active surveillance started in 2000 as a record of demographic and health events including Pregnancies, births, migration events and deaths. It is maintained by 4-monthly homestead visits within 15 locations of the 40 sub-locations within KC(39). KHDSS has 260 000 residents and was identified to capture the majority of patients admitted to KCH. Being the main referral hospital within Kilifi County, KCH receives admissions both within and outside KHDSS (39). Hospital admission data is linked with KHDSS surveillance data by a unique identifier making it easy to know the events of each participant.

Study design

The study was a retrospective cross-sectional study that used prospectively collected clinical and laboratory data of children aged between 2 months and 13 years admitted at KCH for the period between 2002-2018. Children less than 2 months were excluded from the study because of their inability to localize painful stimuli which is important in assessing coma(12) . Children admitted with aNTC were identified using a BCS of <3 that persisted for more than 30 minutes after hypoglycaemia correction (28, 40). BCS is a score of coma status based on assessing verbal, motor and eye as modified Glasgow coma scale (5).This measure is preferable in areas where malaria is endemic such as Kilifi due to its simplicity and improved inter-observer agreement among medical officers (41). We then excluded children with other conditions other than aNTC. CM and ABM are considered common causes of aNTC. Children without ABM or CM indication and no history of trauma were regarded as CUC (32). Data obtained from laboratory test was linked to the study participant clinical data using a unique identifier. Clinical data from the database included the following: Date and time of admission and discharge; Demographic characteristics such as age and sex; Anthropometric measurements including weight, height, and the mid-upper arm circumference (MUAC); Clinical signs and symptoms; Duration of illness and outcome; Laboratory results of complete blood count; Blood culture, malaria slide results and CSF culture (including CSF leucocyte count and CSF antigen test results).

Acute non-Traumatic Coma (aNTC) subgroups

The children were grouped according to 1) malaria slide result as (MPS) positive, negative, or not done (ND), 2) Malaria parasite density cutoff of ≤2500 parasites/µl of blood, 3) whether lumbar puncture was done 4) CSF culture/antigen test result, 5) CSF leukocyte count and 6) blood culture result. Using combinations of the above parameters, four broad groups; Meningitis, CM, CUC and Ungrouped coma were identified. The ungrouped coma consisted of children who could not be categorized among the meningitis, CM, or CUC using available data. Except for the ungrouped coma, each group consisted of definite, highly likely and possible subgroups which were finally collapsed into the respective group and were defined as detailed below and in appendix 3.

Meningitis:

Definite meningitis comprised children with a positive CSF culture or antigen test specifically for *Streptococcus pneumonia*, *Haemophilus influenza*, *Neisseria meningitis* and *Cryptococcus neoforms.* *Highly likely meningitis* group consisted children with undetermined malaria slide results or malaria parasite density ≤2500 parasites/µl and a positive CSF culture or antigen test. *Possible meningitis* children included children either of the following sub-categories: (i) Children with malaria parasite density ≤2500 parasites/µl with undetermined CSF culture and negative antigen test having a CSF leucocyte count ≥10 cells/µl and blood culture positive results , (ii) Those with malaria negative or ND with a negative CSF culture/antigen test and a CSF leucocyte count ≥10 cells/µl plus positive blood culture results (iii) Children with malaria negative results or ND a negative or undetermined CSF culture/antigen test and a CSF leukocyte ND plus positive blood culture result, (iv) children with no malaria results but with a negative CSF antigen/culture test, a CSF leucocyte count ≥10 cells/µl, and positive blood culture results . (v) Children with no malaria results with a negative CSF antigen/culture test and no results for CSF leukocyte counts plus positive blood culture result.

Cerebral Malaria (CM)

Definite CM comprised of children who had had a positive malaria slide results with a parasite density of >2500 parasites/µl (42). CM is defined according to WHO as coma in a child with malaria parasitemia in the absence of an alternative explanation for the cause of illness(31). Highly likely CM consisted of children who had malaria positive results, parasite density >2500 parasites/µl, no LP done and with negative blood culture results. *Possible CM* consisted of children having malaria positive slide results with parasite density of ≤2500 parasites/µl but with a negative or undetermined CSF culture or antigen test results as well as CSF leukocyte count <10 undetermined CSF leukocyte count.

Coma of unknown cause (CUC)

KCH had no capacity to carry out imaging studies using CT or MRI or determine viral encephalitis (5). CUC was defined previously as acute non-traumatic cases that had no CM or meningitis thus no clearly defined cause of their impaired consciousness(32). In this study, we refined the definition of this group as follows;

Children classified as *definite CUC* were those who had negative malaria slide results, had a negative or undetermined CSF culture/ antigen test results, or a leucocyte count <10 cell/ul as well as negative blood culture results. *Highly likely CUC* included children with i) a combination of malaria slide negative results/not determined, negative or undetermined CSF culture/ antigen test results, <10 cell/µl CSF leucocyte count and undetermined blood culture, and ii) a combination of malaria slide negative results/not determined, negative or undetermined CSF culture/ antigen test results, ≥10 cell/µl leucocyte count and negative blood culture results. *Possible CUC* was defined by a combination of several factors including: *i)* a combination of malaria positive slide results with a parasite density ≤2500 parasites/µl, LP done, negative or undetermined CSF culture/ antigen test results, <10 cell/µl CSF leucocyte count and negative/undetermined blood culture results, b) a combination of malaria positive slide results with a parasite density ≤2500 parasites/µl, LP done, negative or not determined CSF culture/ antigen test results, ≥10 cells/µl CSF leucocyte count and negative/ not determined blood culture results and c) Combination of negative malaria slide results, no LP and negative blood culture results.

Data Analysis

The data was obtained in a de-identified format with a unique identifier assigned to each participant. Data analysis was performed using STATA version 15.

Children between 2 months and 13 years admitted in KCH between the period 2002 to 2018 were identified. We then identified the aNTC cases by obtaining the annual frequency of those with meningitis, CM, CUC and ungrouped coma. Overall proportion of children admitted due to meningitis, CM, CUC and ungrouped coma was calculated. The summary statistics, frequency tables of the demographic characteristics were done using the repeated measures tabulation and frequency statistics. Continuous variables are summarised using mean and standard deviation while categorical variables are summarised as counts and percentages.

A regular time series data was used to explore the temporal patterns of aNTC and describe the annual trend of aNTC due to CM, meningitis and CUC over the period 2002 to 2018. To identify changes in acute non-traumatic coma trends, joint point regression was estimated using the Joint Point Regression program. Joint point regression is used to identify the timepoints when changes in the outcome occur by calculating the timepoint percentage change together with its average. Additionally, temporal patterns were explored by fitting an Autoregressive integrated moving average (ARIMA) model. To do this we defined a regular time series plot using monthly counts of CUC related admissions. A line plot of time series was done for the period 2002 to 2018 after examining whether there was seasonality in CUC admissions. Stationarity is one of the main assumptions of time series which is that the mean, variance and autocorrelation does not change over time. To test for stationarity of our model, Augmented Dickey-Fuller unit-root (ref) was used. The null hypothesis for this test is that the series has no root or there is no trend in the model. Auto-Correlation Function (ACF) for the Moving-Average (MA) lags, and Partial Auto-Correlation Function (PACF)(43, 44) for the Auto-Regressive (AR) lags were then used to examine the stationarity series. This was followed by fitting the ARIMA model and seasonal ARIMA model. To determine seasonality, we used the Barlett's formula (43, 44) and selected peaks. The

Portmanteau test was used to confirm the significance of the seasonality as a covariate. We then obtained the appropriate parameters and defined our model.

The association between clinical risk factors of in hospital mortality among CUC was determined by calculating the Odd ratios (ORs) and 95% CIs in binary logistic univariate. Univariable logistic regression was done to describe the association between the risk factors and mortality. We then included risk factors that were statistically significant (p value < 0.05) in the multivariable logistic regression model. We compared model fit using the AIC values and selected the model with the lower value as the best model.

The annual proportion of aNTC due to meningitis, CM and CUC for the cases who were KHDSS residents and non-residents was calculated. Incidence estimates were calculated only among residents within the KHDSS geographical area and were determined by dividing the number of admissions by person years. We also obtained the incidence of CUC according to age and sex by determining the number of admissions by age and sex who reside in the KHDSS divided by the sex and age specific person years.

Since admissions in KCH are both from within and out of KHDSS, we selected only cases from within KHDSS. These cases were then added to obtain the annual coma cases in the KHDSS (See appendix 4). To assess the rate of occurrence of CUC among children admitted in KCH hospital incidence rate among DSS residents was determined by dividing the number of admissions by person years. Person years was obtained by taking into account the number of people in the study and the amount of time each person has contributed to the study.

Ethical consideration

The study was approved by the KEMRI Scientific and Ethics Review Unit (KEMRI/SERU/CGMR-C/129/3715). Further approval was sought from the Human Research Ethics committee at the University of Witwatersrand (REF: M200102). See appendix 1 and 2

RESULTS

Between April 2002 and December 2018, there were 72,112 children admitted at KCH of which 77% (55,642) were aged between 2 months and 13 years. Among these, 7% (3,590) were classified as aNTC. Upon classification 41% (1469) were grouped as CUC while 2% (74) and 42% (1507) were classified as Meningitis and CM respectively (Figure 1). 15% of children who had aNTC could not be categorized in any of the clinical groupings and were classified as ungrouped coma (Figure 1). During the study period, 22% (325) of children with CUC died while 47% (35) and 15% (220) of the children admitted with CM and meningitis died respectively (Table 1). Approximately 50% of aNTC were residents within KHDSS (Table 1)

Admission data was subcategorized according to children from the KHDSS and outside. Of the 1469 CUC cases, 797 (54%) were non-residents while 672 (46%) were KHDSS residents. Among the 74 meningitis cases 48 (65%) were non KHDSS and 26 (35%) were from KHDSS. Overall CM cases were 1507 which included 749 (49.7 %) as non KHDSS residents while 759 (50.3 %) as KHDSS residents (see table 1).

aNTC Cases Data Flow Diagram

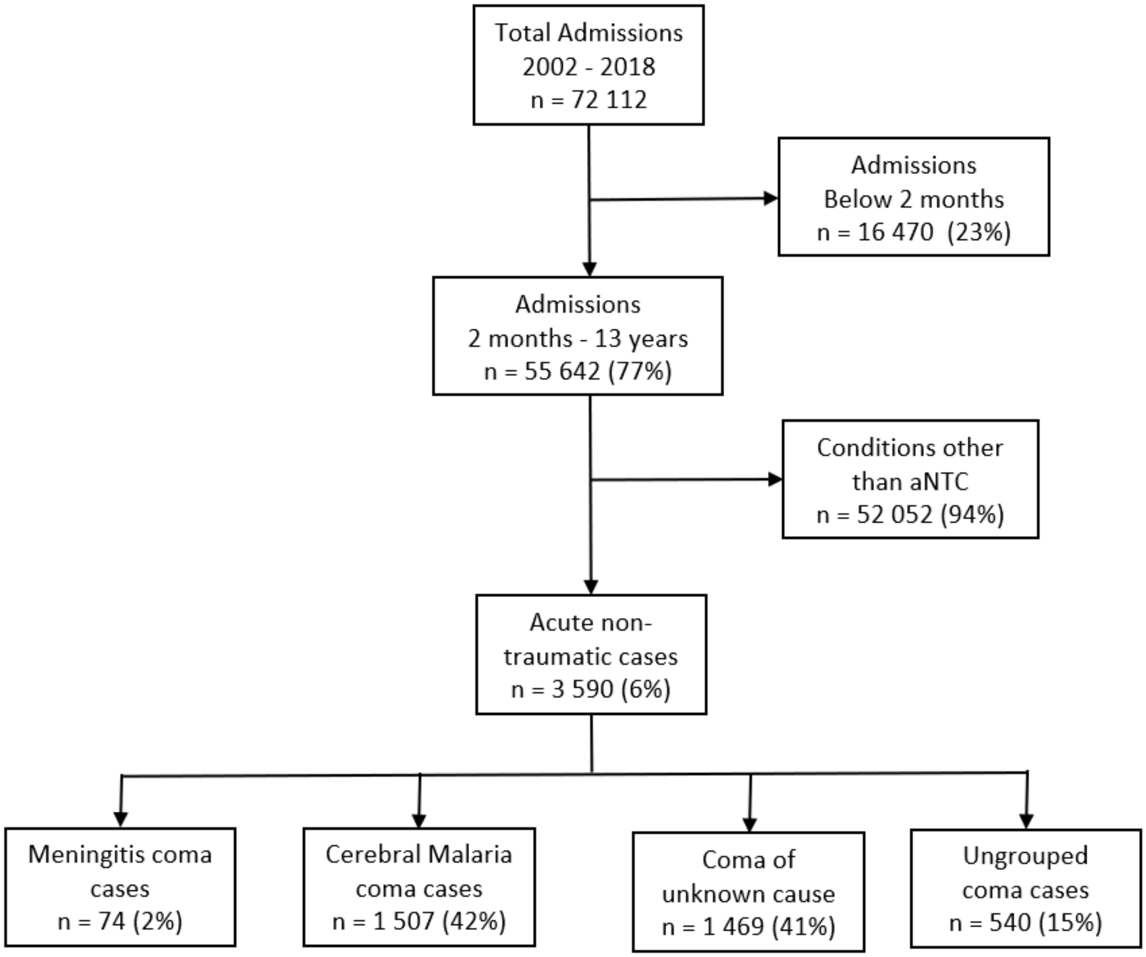

Figure 1: aNTC cases selection summary: *A flow chart showing the selection of study participants among children between 2 months and 13 years admitted at KCH for the period 2002 – 2018. aNTC cases were categorized as meningitis, CM, CUC and ungrouped coma cases.*

Table 1: Characteristics of study participants

	All	Meningitis	Cerebral malaria	Coma of unknown cause	Ungrouped
Gender N(%)					
Female	1658	39 (53)	712 (47)	651 (44)	256 (47)
Male	1932	35 (47)	795 (53)	818 (56)	284 (53)
Age					
<1 yr	744	42 (57)	100 (7)	430 (29)	172 (32)
1-2 yrs	1251	7 (10)	569 (38)	495 (34)	180 (33)
3-5yrs	985	5 (7)	560 (37)	321 (22)	99 (18)
6-13 yrs.	610	20 (27)	278 (18)	223 (15)	89 (16)
Case definition					
Definite	1385	42 (57)	881 (59)	462 (31)	
Highly likely	300	12 (16)	235 (16)	53 (4)	
possible	1375	20 (27)	391 (26)	964 (65)	
Status					
Deaths	835	35 (47)	220 (15)	325 (22)	255 (47)
Alive	2742	39 (53)	1281 (85)	1141 (78)	281 (52)
Residence					
KHDSS	1702	26 (35)	758 (50)	672 (46)	246 (46)
Non KHDSS	1888	48 (65)	749 (50)	797 (54)	294 (54)

Proportion and trend of admissions of aNTC

The proportion of admissions of CUC among aNTC cases increased from 2002 reaching a peak between 2008 and 2009. However, during the same period, the proportion of CM cases reduced while no major changes were observed among those for meningitis and the ungrouped. Between 2009 and 2012, there was a decline in the proportion of CUC while that for CM and the ungrouped increased. The period from 2013 to 2018 reported an increase in the proportion of CUC with a concomitant reduction in the proportion of the ungrouped aNTC and CM (Figure 2). Overall, the proportion of children admitted with Meningitis and CM reduced over time while that represented by CUC increased demonstrating a rise in the burden of CUC. Joint point regression analysis identified two joint points leading to three periods: period 1; 2002 – 2009, period 2; 2009 – 2012 and period 2012 – 2018 (Figure 3). Between 2002 - 2009, a gradual rise in the number of CUC admissions was observed which was then followed by a decline in the cases was observed between 2009 – 2012 then finally a sharp rise in the cases was observed between 2012 -2018. In CM and meningitis an overall downward trend was observed apart from a slight rise in CM between the period 2008 - 2015.

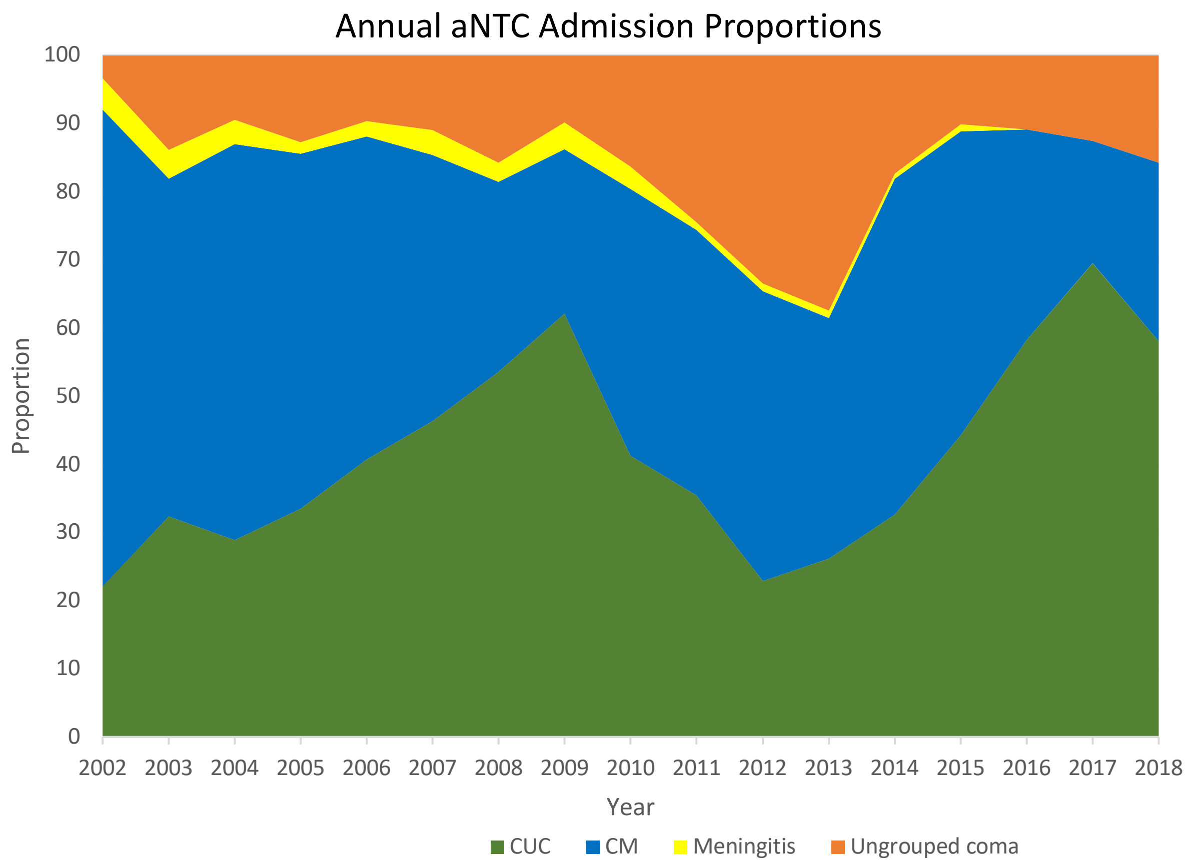

Figure 2: aNTC annual admission proportions*: Overall, there is an increase in the proportion of children with CUC as the proportion of meningitis and CM decreases.*

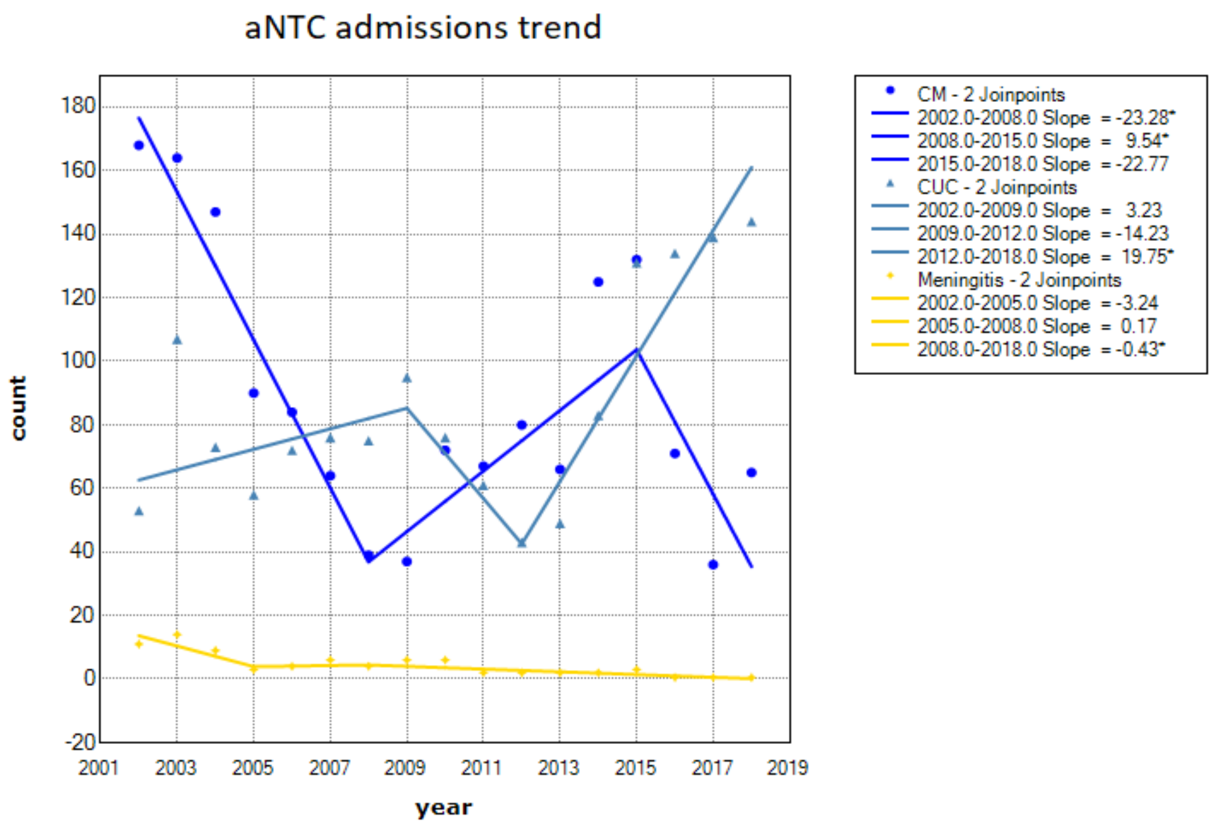

Figure 3: Jointpoint aNTC admission trend. *There is a decrease in trend of meningitis admission. CM shows a decrease in the period 2002-2008 then an increase between 2008-2015 followed by a decrease between 2015-2018. There is an increase in CUC between 2002-2009 followed by a decrease between 2009-2012 then an increase in the period 2012-2018*

To test whether there was a seasonal pattern among admissions of CUC, we performed a monthly temporal analysis for CUC for the period 2002 to 2018. Figure 4 shows a time series plot for the monthly number of admissions due to CUC. Autocorrelation analysis showed different peaks of the monthly transformed series. Portmanteau test for white noise was used to test for seasonality with a significance of ($p = 0.0014$). Comparing a seasonal autoregressive integrated moving average model (1,0,1,7) and autoregressive integrated moving average model (1,0,2) using the Akaike Information Criteria (AIC), the ARIMA (P, D, Q) model fitted the observed data well.

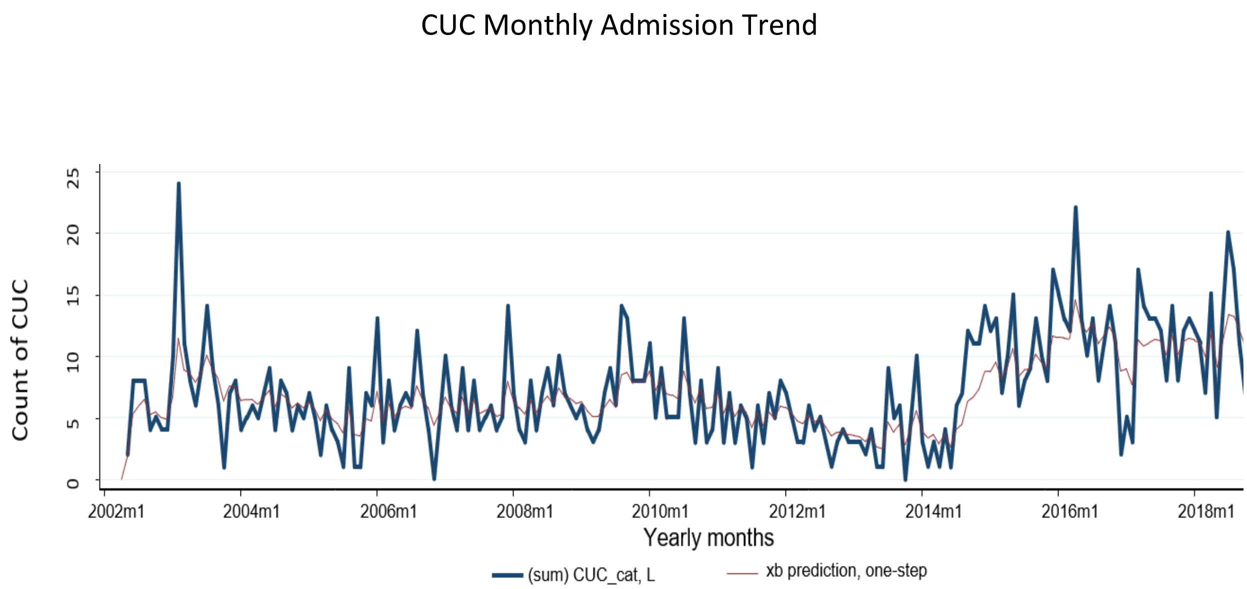

***Figure 4: CUC monthly admission trend**: A graphical plot showing monthly number of admission trend for CUC over the period 2002 – 2018. This is a time series plot for the monthly CUC admissions at KCH. The graph shows a prediction using ARIMA model.*

aNTC mortality trend over time

We calculated the annual proportion of deaths among the four groups within the aNTC to determine whether CUC was associated with an increased risk of death compared to CM or meningitis. Proportion of CUC deaths increased from 23% in 2002 to 51% in 2009 followed by a decrease to 2012 then an increase up to 69% in 2017.Highest proportion of CM deaths was 55% in 2002 which then decreased to 32% in 2003 followed by a 46% increase in 2004. A decrease in CM death proportion is then observed between the period 2004 to 2008 then a slight increase followed by a decrease of 33% in 2014 to 8% in 2017. Meningitis proportion of death showed a decrease with 15% in 2002 and 2% in 2014. As shown in figure 5, overall, CUC was associated with elevated deaths over the years. Additionally, while death due to meningitis and CM showed a decreasing trend, that associated with CUC declined then sharply rose from 2013 to 2017 (Figure 5).

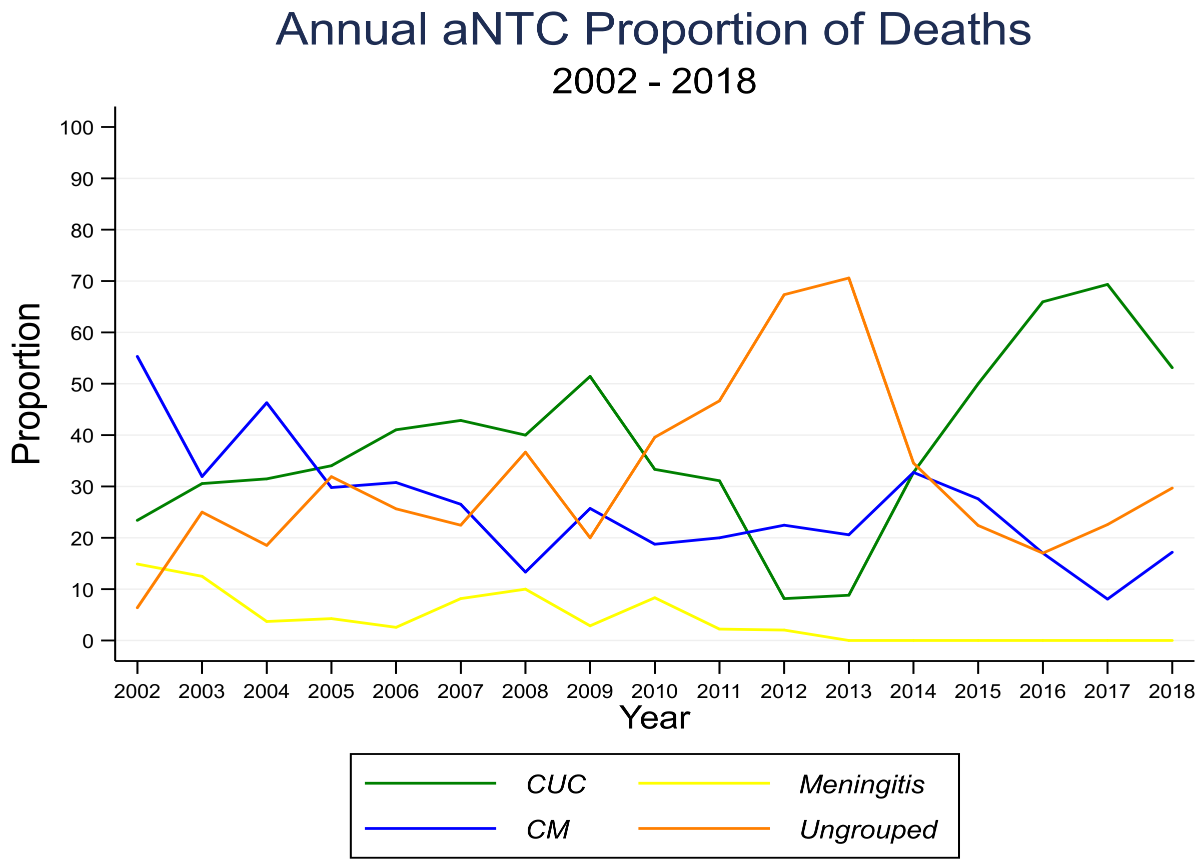

Figure 5: Proportion of death for aNTC. *This illustrates the trend in proportion of deaths due to aNTC for children between 2 months and 13 years admitted at KCH for the period 2002 - 2018.The different colors in the legend indicate CUC, CM, meningitis and ungrouped aNTC categories. Overall, CUC deaths increased during the study period while CM and meningitis proportion of deaths decreased*

Risk factor analysis for CUC mortality

We then investigated clinical features associated with inpatient mortality among children with CUC. Thirty of the clinical features, analysed by univariable logistic regression, were associated with mortality (Appendix 5). These included features such as HIV, diarrhea, vomiting, difficulty in breathing and irregular respiration (all p <0.001). All the significant variables in the univariable analysis were retained for further analysis in the multivariable logistic regression. Clinical features associated with mortality were MUAC (OR=0.6), hypoxia (OR=0.1), lymphadenopathy (OR=55) and irregular respiration (OR=14) (all p <0.001, Table 4)

Table 2*: Multivariate analysis to determine predictors for death in children admitted in coma in Kilifi County Hospital in Kenya between 2002 and 2018*

Characteristic	OR (95% CI)	p-Value
MUAC	0.579 (0.346, 0.970)	0.038
Hypoxia	0.073 (0.021, 0.247)	<0.0001
Lymphadenopathy	55.320 (5.242, 583.821)	0.001
Irregular respiration	14.065 (3.076, 64.310)	0.001

Footnote: Odds ratio (OR) are provided with Cis in brackets and a p value. Multivariable logistic regression results provided. The table shows only the significant variables in the multivariable logistic regression with extended results provided in the appendix. MUAC is a continuous variable while hypoxia, lymphadenopathy and irregular respiration are categorical variables with "No" as the reference.

The Incidence of CUC within the KHDSS geographical area

In the study we examined the incidence of CUC in comparison to meningitis and CM. Over the study period, the incidence rate of CUC among KHDSS residents was 36 per 100,000-person years. Additionally, we plotted the incidence of meningitis, CM and CUC related aNTC in the KHDSS as shown in figure 6. Between 2002 – 2003 we observed an increase in incidence of meningitis, CM and CUC followed by a decrease between 2003 – 2005. We then observed a slight increase in up to 2006 then CUC tends to decrease until 2012 then increase between the period 2012-2018. Meningitis shows a decrease between the period 2006-2018 as CM decreases between 2006-2008 then increases up to 2014 and eventually decreases until 2017. We observed a general upward trend in CUC in the 2012 to 2018 as the incidence of meningitis and CM related coma decreased.

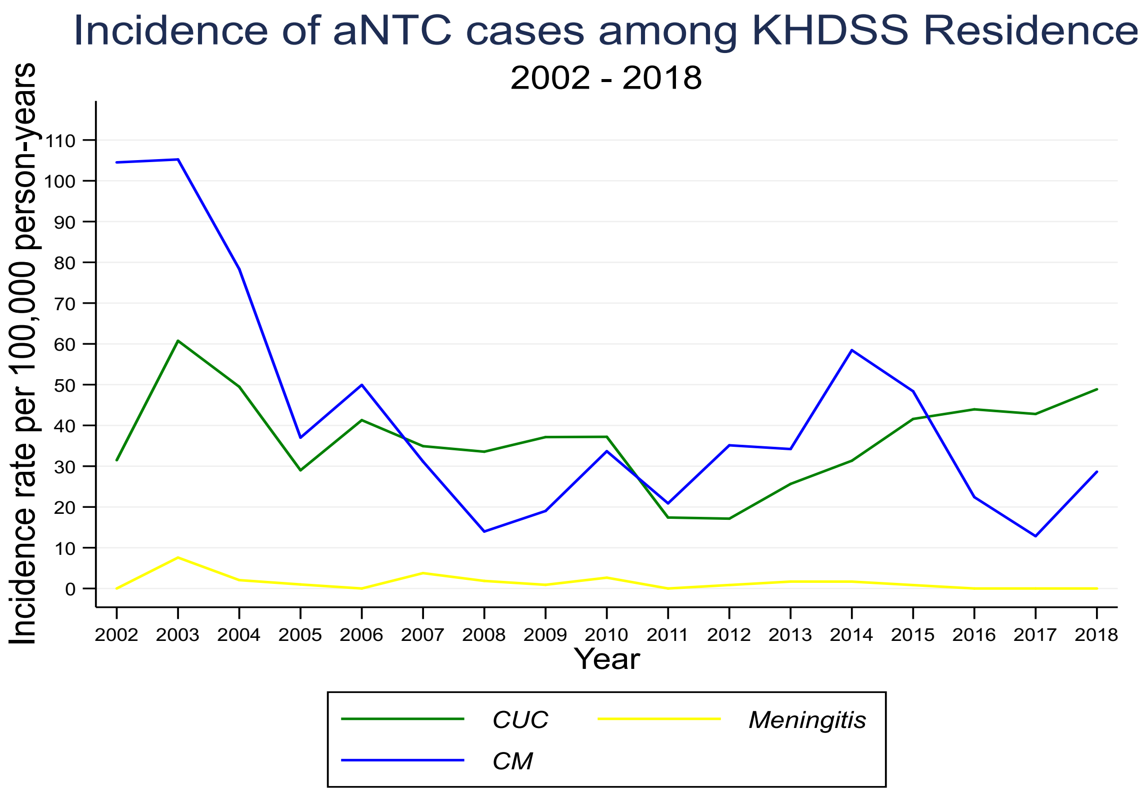

Figure 6: Incidence of aNTC within KHDSS geographical area. *Incidence rates per 100,000 person years for KHDSS children admitted at KCH for the period 2002 – 2018. We calculated the incidence rate by taking the number of cases per year divided by the specific person years. The different line plots indicate subdivision of aNTC in CUC, CM and meningitis (see legend for color definition).*

Annual incidence of deaths among KHDSS children admitted at KCH showed a lowest incidence rate of 8 per 100,000 person years while the highest incidence during the study period was in 2003 with 34 per 100,000 person years (Table 3).

Table 3: Annual Incidence and case death of childhood aNTC between 2002 to 2018

Year	**Annual Incidences/100,000 children**	**95% CI**	**Case Death (n)**
2002	8	4 to 20	6
2003	34	25 to 52	31
2004	24	16 to 37	23
2005	20	12 to 31	20
2006	18	10 to 27	19
2007	20	12 to 29	21
2008	12	6 to 20	13
2009	14	7 to 21	15
2010	19	10 to 26	21
2011	12	5 to 18	14
2012	17	8 to 23	20
2013	10	4 to 16	12
2014	24	13 to 30	28
2015	15	7 to 21	18
2016	8	3 to 14	9
2017	18	9 to 24	21
2018	20	10 to 26	24

Footnote: Annual incidence and case deaths for children who reside in KHDSS geographical area but were admitted in KCH. Incidence rate of this participants was obtained by dividing the number of cases and person years. Confidence interval of the incidence rates also provided in the brackets.

DISCUSSION

The objective of this study was to investigate the incidence and mortality among children presenting with acute non-traumatic coma of unknown cause in Kilifi county between 2002 and 2018. Our results show that CUC comprises a large proportion (41%) of children admitted at KCH with aNTC. Based on the classification we also found that most CUC were in the possible category 964 (65%) as compared to the definite and highly likely categories. We also show that the proportion of admissions of CUC among aNTC have been increasing from 2002 to 2018 while that for those with a diagnosis for CM and ABM have been declining. We noted that the increase in CUC was not related to seasonality. We report an incidence of 36 per 100,000-person years among children with CUC that reside with KHDSS. Finally, we showed that there was an increase in the proportion of deaths among CUC over time compared to other causes of aNTC. Mortality among children admitted with CUC was associated with low MUAC, hypoxia, lymphadenopathy and irregular respiration.

A steady rise in the number of CUC admissions was observed over time from 2002 - 2009 with a dip in the cases between 2009 – 2012 then an increase between 2012 -2018. CM and meningitis witnessed an overall downward trend save a slight rise in CM in 2008 – 2015. Overall malaria transmission seems to influence CUC admissions an aspect also observed by Gwer(12). The results indicate that interventions that have been put in place to control spread on malaria and meningitis have had a significant impact. However, aNTC due to unknown cause remains a problem.

The average incidence of 36 per 100,000 children with CUC reported here is lower than that reported previously by Gwer et al of 93/100 000 children in 2004 that declined to 44/100 000 children in 2009. We observed an increase in the incidence of CUC from 2011 to 2018 among children resident in KHDSS residents while that for meningitis and CM decreased. Age stratified incidence analysis showed that younger children had a higher incidence rate compared to the older children. Younger children are more prone to poor outcome following infectious insults and the higher incidence among the younger age groups may reflect lack of immunity to such infections.

Our results show that 22% of children with CUC died during the inpatient period which was higher than that recorded for CM but lower than that for meningitis and ungrouped aNTC. Margins of similarly high mortality were observed in India (40%), Pakistan (35%) and Saudi-Arabia (60.5%)(19, 20, 22). Further analysis showed several clinical features that were significantly associated with mortality due to CUC in univariate analysis. These features including HIV, diarrhea, vomiting, difficulty in breathing and irregular respiration likely indicate that coma may also arise from enteric and systemic infections including pneumonia and sepsis. When these features were subjected to multivariate analysis, MUAC, hypoxia, lymphadenopathy, and irregular respiration were the only significant features associated with mortality. Low MUAC reflects poor nutritional status among children is a well-established marker for mortality due to infectious diseases among children. The additional features including hypoxia, irregular respiration, and lymphadenopathy point to underlying undiagnosed infectious causes of mortality among children with CUC. Gwer at al observed an overall mortality of 25% with a number of factors including bradycardia, clinical signs of meningitis ,deep coma and bacteraemia were independently associated with an increase in the risk of death(5). Children with a history of seizures within 24 hours before admission and malaria parasitaemia were independently associated with reduced risk of death with no evidence that the risk factors for death varied with year(5).

Introduction of vaccines such Haemophilus influenza B conjugate vaccine and PCV has been associated with a significant decrease in meningitis. *Haemophilus influenza* B vaccine was associated with a reduction in *Haemophilus influenza* B meningitis while introduction of Pneumococcal vaccine also resulted to a significant reduction in ABM (8, 45, 46). This is also seen in our analysis as the trend in coma due meningitis is reducing over time. It is therefore evident that vaccine intervention has changed the outcome and aetiology of coma in sub-Saharan Africa. Malaria transmission changes in the Coast region are also due to introduction of interventions such bed nets and use of anti-malaria drugs (13). This has also impacted on the transmission of malaria thus can be attributable to the reduction of coma due to cerebral malaria over time. The above findings demonstrate the importance of identifying the etiology of CUC in order to develop suitable treatment and preventative measures to manage and control CUC.

Our study had some limitation, based on our analysis the incidence of aNTC was only reported for children who were admitted in KCH but reside in KHDSS. This was a limitation since person years are only available through the surveillance system that is ongoing in KHDSS. By nature of this limitation it is possible that the reported incidence is an underestimate to the actual overall incidence of aNTC in KCH. There is a possibility of other epidemiological factors which are yet to be investigated but play a role in this increased incidence. Since the design of our study was cross sectional, we did not include deaths that occurred after discharge and this could underestimate mortality estimates.

CONCLUSION

Our data indicates a general reduction in aNTC related to CM and meningitis as CUC increased over the study period. With the decline in malaria transmission and introduction of vaccines against *Haemophilus influenza* and Pneumococcus, there has been a decline in hospital admission due to CM and Meningitis. These declines have been accompanied by a significant rise in admissions due to CUC. Therefore, understanding the etiology of CUC is critical in improving diagnosis and treatment, and in developing preventive measures which can ultimately reduce incidence and improve hospital outcome.

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CHAPTER 3: EXTENDED METHODOLOGY

Study setting

The study utilised data from children admitted in Kilifi County Hospital between 2002 and 2018. A paediatric intensive care unit is lacking in the hospital and the region as a whole. Approximately 80% of the pediatric admission come from two-thirds of the residence in Kilifi District that consist of 15 locations around the hospital (1). Map of the KHDSS site is shown in appendix 6.

The KHDSS was launched in 2000 is managed by the KEMRI-Wellcome Trust Research Programme accounts for a well characterised population aimed at defining rates of migration, fertility and mortality. Population register in KHDSS is updated in a four monthly visit basis. Additionally admission and mortality events from KCH are also updated on a real time basis (2). The admission data was linked with the surveillance data by a unique identifier making it easy to know the events of each participant.

Data Quality

Data on morbidity and mortality events was collected using direct electronic data capture updated by qualified medical officers then electronically synchronised to a MYSQL database from the point of collection in the clinics. Data quality checks were implemented in the system to reduce human error during data entry. Incoming admissions data was linked in real time with surveillance data by field workers who match the data. Field workers have a unique access to the system and use clearly pre-defined procedures to match the patients (2).

The data was de-identified, and a unique identifier was assigned to each participant. Further data quality checks were done to identify any discrepancies. Daily backup was done on the database and each admission event has a unique identifier. All data is stored in a password protected and encrypted computer. Data analysis was performed using STATA version 15 and R.

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Appendices

Appendix 1: Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Emily Odipo (Student number: 2103465) am a student registered for the degree of Msc. Biostatistics in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: ______________ Date: 08/12/2020

1

Appendix 2: Turnit report

Appendix 2: Turnit report **14-12-2020**

2103465:Research_report_7th_dec_final(1).docx

ORIGINALITY REPORT

14%	13%	11%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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3	wiredspace.wits.ac.za Internet Source	1%
4	worldwidescience.org Internet Source	1%
5	Omolara Baiyegunhi, Bongiwe Ndlovu, Funsho Ogunshola, Nasreen Ismail, Bruce D. Walker, Thumbi Ndung'u, Zaza M. Ndhlovu. "Frequencies of circulating Th1-biased T follicular helper cells in acute HIV-1 infection correlate with the development of HIV-specific antibody responses and lower set point viral load", Cold Spring Harbor Laboratory, 2018 Publication	1%
6	C P Wong. "Current topic: Incidence, aetiology, and outcome of non-traumatic coma: a	1%

Appendix 3: Ethical clearance Kemri-Wellcome Trust

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel:(254) (020) 2722541, 2713349, 0722-205901, 0733-400003, Fax: (254) (020) 2720030
E-mail: director@kemri.org, info@kemri.org, Website.www.kemri.org

KEMRI/RES/7/3/1 **August 28, 2019**

TO: **JAMES MWANGI NJUNGE**
PRINCIPAL INVESTIGATOR

THRO' **THE DIRECTOR, CGMR-C**
KILIFI

Forwarded: 9/9/19

DIRECTOR
FOR GEOGRAPHIC MEDICINE
RESEARCH, COAST

Dear Sir,

RE: **KEMRI/SERU/CGMR-C/129/3715 (*REQUEST FOR ANNUAL RENEWAL*): A RETROSPECTIVE STUDY TO INVESTIGATE THE AETIOLOGY AND MOLECULAR BIOMARKERS OF NON-TRAUMATIC COMA OF UNKNOWN CAUSE IN CHILDREN ADMITTED AT KILIFI COUNTY HOSPITAL USING MOLECULAR APPROACHES**

Thank you for the continuing review report for the period **26th September 2018 to 9th August 2019.**

This is to inform you that the expedited review team of the KEMRI Scientific and Ethics Review Unit (SERU) conducted the annual review of the above referenced application and was of the informed opinion that the progress made during the reported period is satisfactory. The study has therefore been granted **approval**.

This approval is valid from **26th September 2019** through to **25th September 2020**. Please note that authorization to conduct this study will automatically expire on **25th September 2020**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the SERU by **14th August 2020.**

You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to the SERU for review prior to initiation. You may continue with the study.

Yours faithfully,

ENOCK KEBENEI
THE ACTING HEAD
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT

KEMRI Centre for Geographic Medicine Res.
RECEIVED
09 SEP 2019

In Search of Better Health

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel:(254) (020) 2722541, 2713349, 0722-205901, 0733-400003, Fax: (254) (020) 2720030
E-mail: director@kemri.org, info@kemri.org, Website.www.kemri.org

KEMRI/RES/7/3/1 **August 19, 2019**

TO: **DR. JAMES M. NJUNGE,**
PRINCIPAL INVESTIGATOR

THROUGH: **THE DIRECTOR, CGMR-C,**
KILIFI

Forwarded: 21/08/19

Dear Sir,

RE: **KEMRI/SERU/CGMR-C/129/3715 *(RESUBMISSION REQUEST FOR 1ST AMENDMENT)*: A RETROSPECTIVE STUDY TO INVESTIGATE THE AETIOLOGY AND MOLECULAR BIOMARKERS OF NON-TRAUMATIC COMA OF UNKNOWN CAUSE IN CHILDREN ADMITTED AT KILIFI COUNTY HOSPITAL USING MOLECULAR APPROACHES**

Reference is made to your letter dated August 05, 2019. The KEMRI Scientific and Ethics Review Unit (SERU) acknowledge receipt of the revised amendment documents on August 08, 2019.

This is to inform you that during the 289th Committee A meeting of the KEMRI Scientific and Ethics Review Unit (SERU) held on **July 09, 2019** are adequately addressed.

You are therefore **authorized** to implement the following Amendments accordingly:

1) Amended to determine the aetiology of non-traumatic coma of unknown cause (CUC) overtime in children admitted at Kilifi county hospital from 2002-2018 instead of the previously approved 2002-2014. To achieve this, we request to analyze clinical data and samples collected under protocol SSC 1433.
2) Inclusion of Antony Scott; the PI of SSC 1433 as an investigator.

Please note that you are responsible for submitting any further changes to the approved version of the study protocol to SERU for review and the changes should not be initiated until written approval from the SERU is received.

Yours faithfully,

ENOCK KEBENEI,
THE ACTING HEAD,
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT.

KEMRI Centre for Geographic Medicine Research - Coast
RECEIVED
21 AUG 2019
Tel: 0709983676/77
P.O. Box 428, Kilifi

In Search of Better Health

Appendix 4: Ethical Clearence- University of Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Ms EA Odipo
School of Public Health
Medical School
University

E-mail: 2103465@students.wits.ac.za

CC: Supervisor: Professor E Musenge; Drs J Njunge & A Abdi
<Eustasius.Musenge@wits.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/02/21

REF: *R14/49*

PROTOCOL NO: M200102 *(*This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study*)*

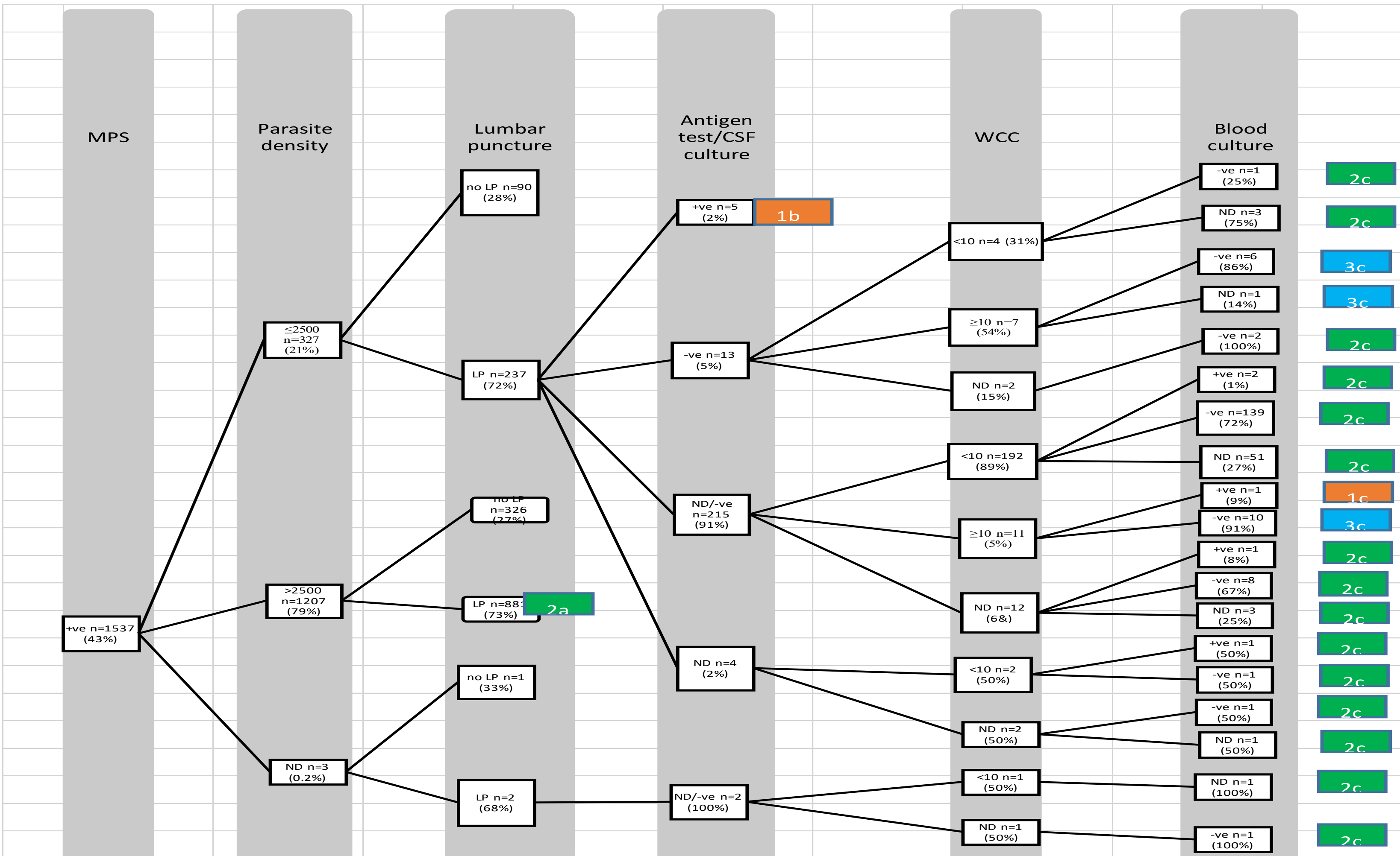
PROJECT TITLE: *Incidence and mortality of childhood non-traumatic coma of unknown cause in Kilifi County between 2002 and 2018*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

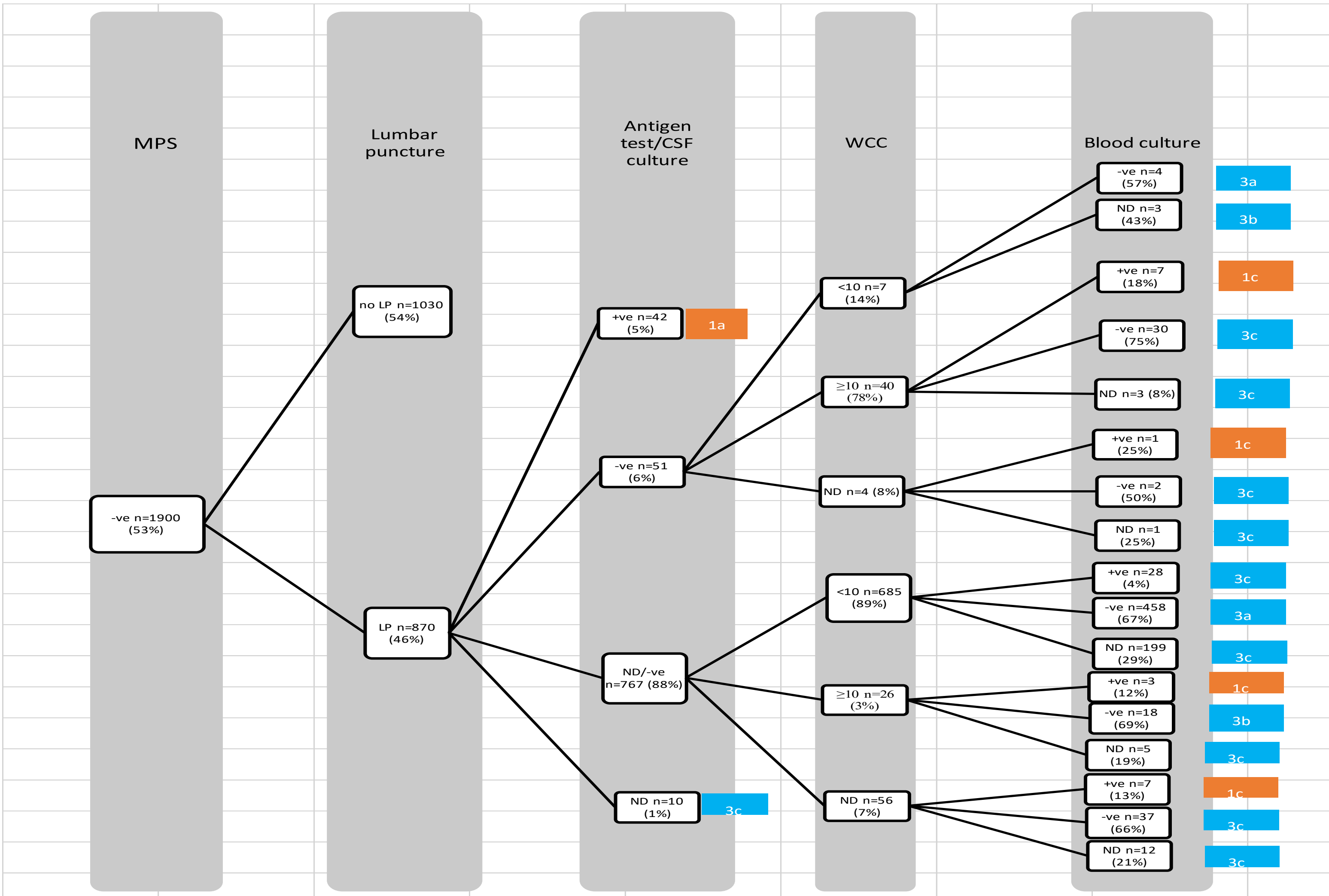
MSWorks2000/Iain0007/Clearscan.wps

Appendix 5: aNTC case definition

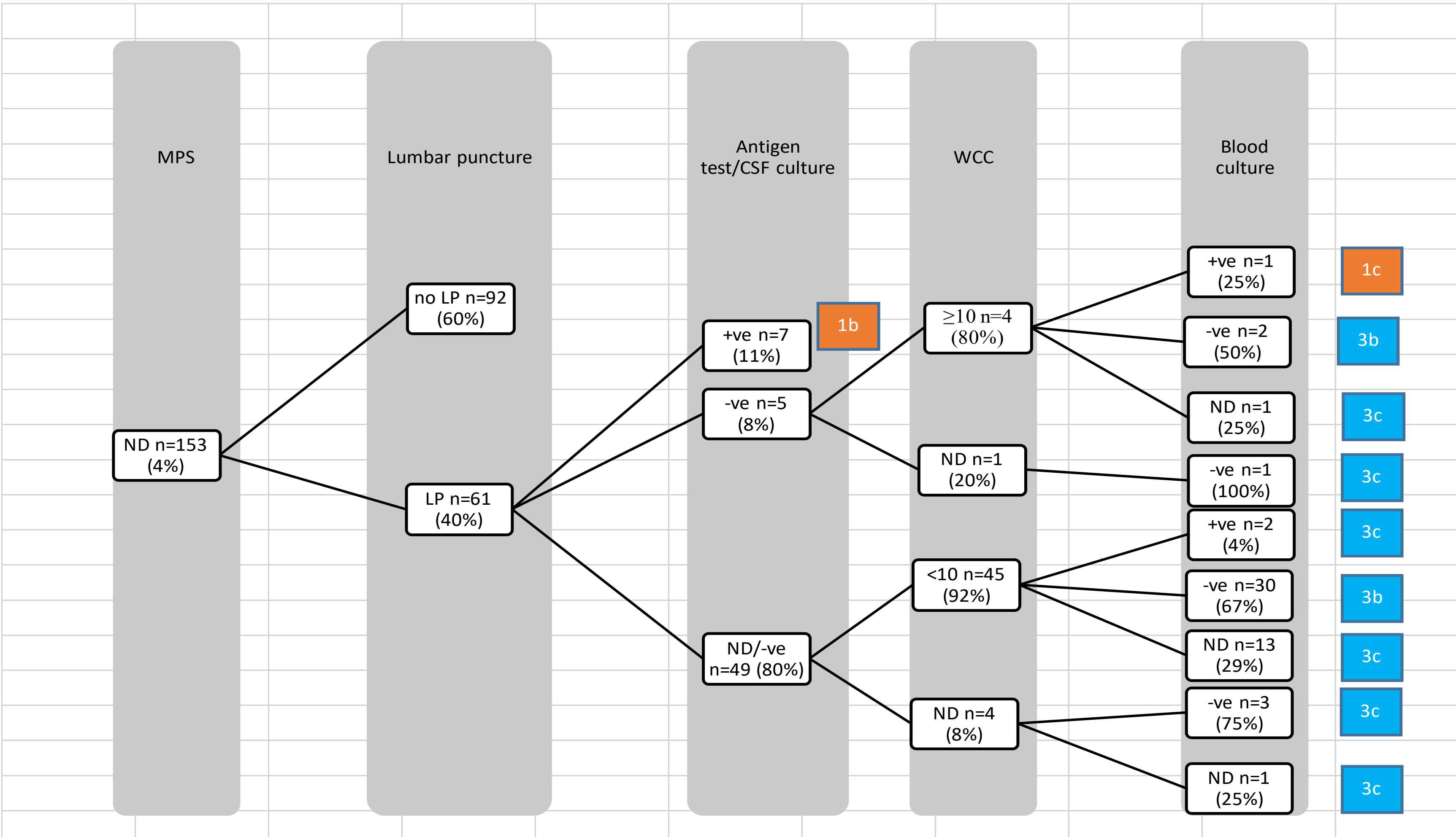
Malaria positive participants' subdivisions



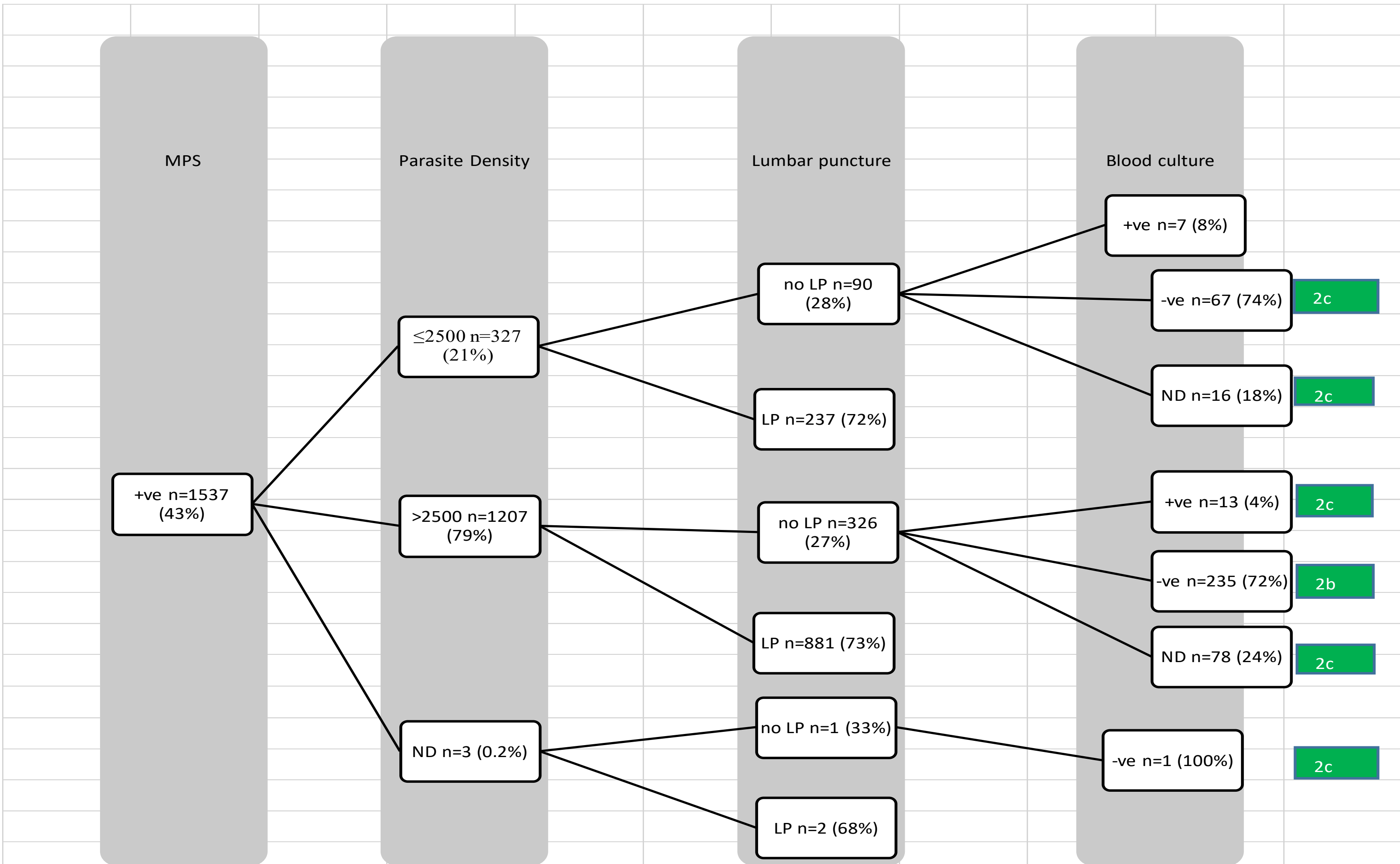
Malaria negative participants' subdivisions



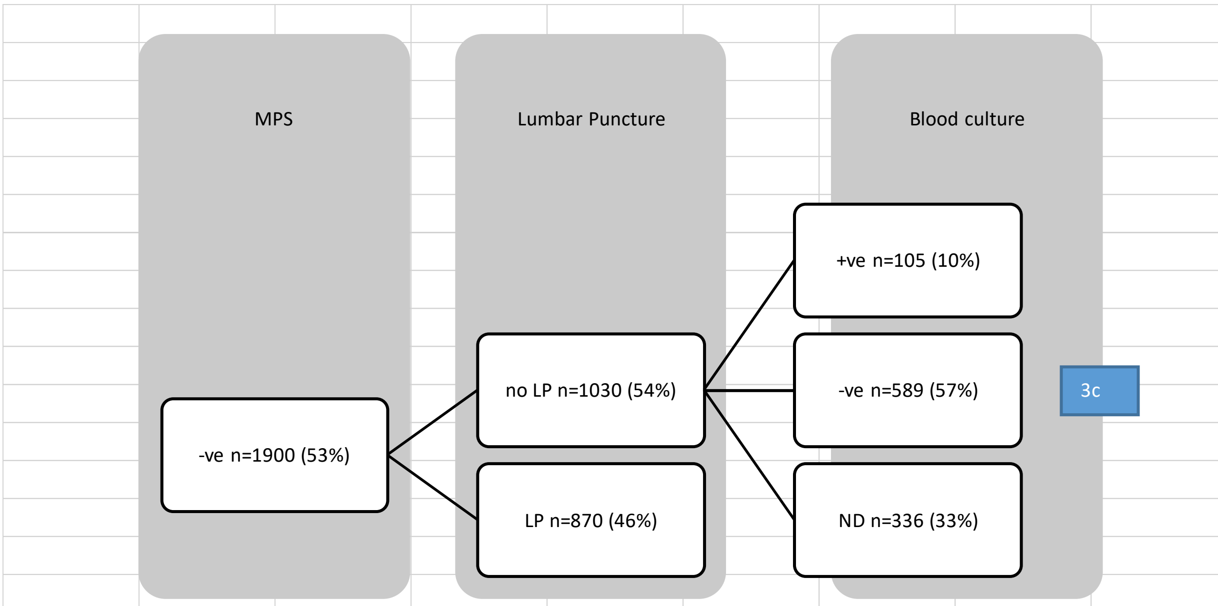
Undetermined malaria results subdivisions



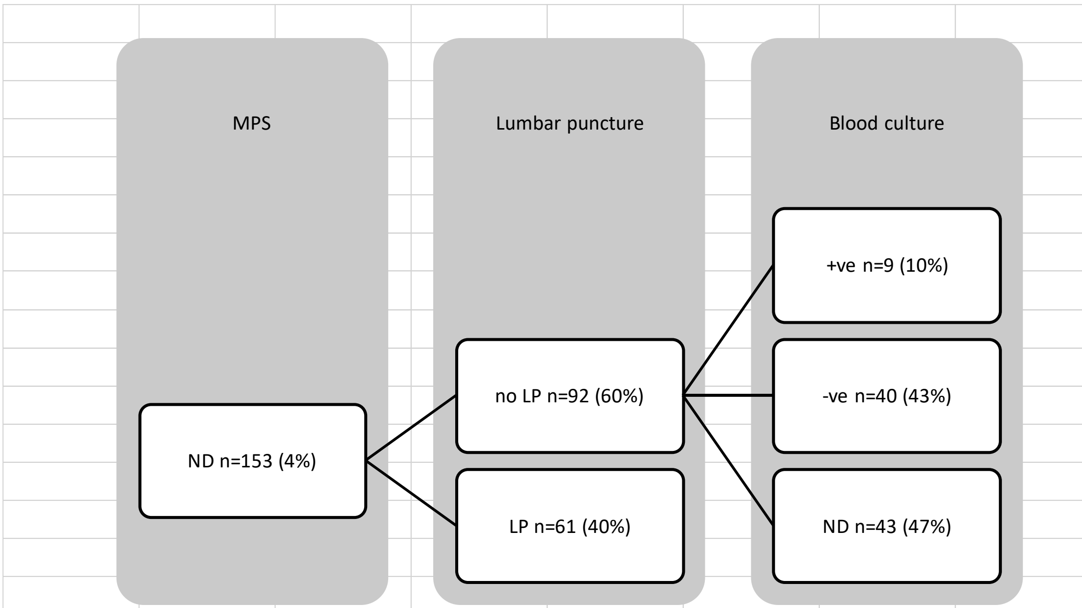
Malaria positive- no lumbar puncture done



Malaria negative- no lumbar puncture done



Undetermined- no lumbar puncture done



Appendix 6: Frequency of coma of unknown cause by year

Year	CUC			Meningitis			CM		
	All cases	Non DSS resident	DSS resident	All cases	Non DSS resident	DSS resident	All cases	Non DSS resident	DSS resident
	n	n (%)	n (%)	n	n (%)	n (%)	n	n (%)	n (%)
2002	53	28 (52.83)	25 (47.17)	11	11 (100.00)	0	168	85 (50.60)	83 (49.40)
2003	107	51 (47.66)	56 (52.34)	14	7 (50.00)	7 (50.00)	164	67 (40.85)	97 (59.15)
2004	73	25 (34.25)	48 (65.75)	9	7 (77.78)	2 (22.22)	147	71 (48.30)	76 (51.70)
2005	58	29 (50.00)	29 (50.00)	3	2 (66.68)	1 (33.33)	90	53 (58.89)	37 (41.11)
2006	72	29 (40.28)	43 (59.72)	4	4 (100.00)	0	84	32 (38.10)	52 (61.90)
2007	76	39 (51.32)	37 (48.68)	6	2 (33.33)	4 (66.67)	64	31 (48.44)	33 (51.56)
2008	75	39 (52.00)	36 (48.00)	4	2 (50.00)	2 (50.00)	39	24 (61.54)	15 (38.46)
2009	95	54 (56.84)	41 (43.16)	6	5 (83.33)	1 (16.67)	37	16 (43.24)	21 (56.76)
2010	76	34 (44.74)	42 (55.26)	6	3 (50.00)	3 (50.00)	72	34 (47.22)	38 (52.78)
2011	61	41 (67.21)	20 (32.79)	2	2 (100.00)	0	67	43 (64.18)	24 (35.82)
2012	43	23 (53.49)	20 (46.51)	2	1 (50.00)	1 (50.00)	80	39 (48.75)	41 (51.25)
2013	49	19 (38.78)	30 (61.22)	2	0	2 (100.00)	66	26 (39.39)	40 (60.61)
2014	83	46 (55.42)	37 (44.58)	2	0	2 (100.00)	125	56 (44.80)	69 (55.20)
2015	131	82 (62.60)	49 (37.40)	3	2 (66.67)	1 (33.33)	132	75 (56.82)	57 (43.18)
2016	134	83 (61.94)	51 (38.06)	0	0	0	71	45 (63.38)	26 (36.62)
2017	139	89 (64.03)	50 (35.97)	0	0	0	36	21 (58.33)	15 (41.67)
2018	144	86 (59.72)	58 (40.28)	0	0	0	65	31 (47.69)	34 (52.31)
Total	1,469	797 (54.25)	672 (45.75)	74	48 (64.86)	26 (35.14)	1,507	749 (49.70)	758 (50.30)

Appendix 7: CUC mortality risk factor analysis

Variable	Alive	Died	Univariable analysis		Multivariable analysis	
	Mean (SD)	Mean (SD)	OR (95% CI)	Pvalue	OR (95% CI)	Pvalue
Weight	11.209 (5.801)	9.226 (5.471)	0.929 (0.889, 0.961)	<0.0001	0.991 (0.721, 1.363)	0.955
Height	87.097 (21.547)	78.294 (21.556)	0.979 (0.971, 0.987)	<0.0001	0.999 (0.879, 1.137)	0.998
Head circumference	46.769 (4.270)	45.146 (4.577)	0.921 (0.892, 0.949)	<0.0001	1.071 (0.838, 1.369)	0.585
Respiratory rate	41.993 (15.036)	49.131 (19.043)	1.026 (1.018, 1.035)	<0.0001	1.065 (0.991, 1.146)	0.088
Heart rate	145.563 (34.928)	148.113 (47.351)	1.002 (0.998, 1.006)	0.377		
Saturation oxygen	92.897 (49.025)	95.516 (90.176)	1.001 (0.999, 1.003)	0.547		
Muac	14.286 (2.352)	13.022 (2.582)	0.789 (0.739, 0.844)	<0.0001	0.579 (0.346, 0.970)	0.038
	n (%)	n (%)				
Decreased skin turgor						
No	1012 (89.01)	249 (76.62)	Ref		Ref	
Yes	125 (10.99)	76 (23.38)	2.471 (1.799, 3.394)	<0.0001	0.300 (0.051, 1.779)	0.185
Fever						
No	408 (35.76)	73 (22.46)	Ref		Ref	
Yes	733 (64.24)	252 (77.54)	1.924 (1.441, 2.569)	<0.0001	1.296 (0.365, 4.597)	0.688
Age group						
< 1 yr	287 (25.15)	142 (43.69)	Ref		Ref	
1 - <5 yr	598 (52.41)	129 (39.69)	0.437 (0.329, 0.578)	<0.0001	3.148 (0.455, 21.797)	0.245
≥ 5 yr	256 (22.44)	54 (16.62)	0.426 (0.298, 0.611)	<0.0001	9.361 (0.342, 256.157)	0.185

Hypoxia						
No	789 (69.76)	201 (62.81)	Ref		Ref	
Yes	342 (30.24)	119 (37.19)	1.364 (1.051, 1.771)	0.02	0.073 (0.021, 0.247)	<0.0001
Tachypnoea						
No	561 (49.65)	109 (34.71)	Ref		Ref	
Yes	569 (50.35)	205 (65.29)	1.851 (1.428, 2.399)	<0.0001	0.742 (0.135, 4.062)	0.73
Capillary refill						
0 - 2 seconds	990 (86.77)	204 (62.77)	Ref		Ref	
≥ 3 seconds	151 (13.23)	121 (37.23)	3.885 (2.921, 5.166)	<0.0001	1.005 (0.162, 6.236)	0.995
Oedema						
No	1128 (98.86)	312 (96.30)	Ref		Ref	
Yes	13 (1.14)	12 (3.70)	3.334 (1.464, 7.594)	0.004	68.180 (3.106, 1496.588)	0.65
Convulsion						
No	336 (29.45)	180 (55.38)	Ref		Ref	
Yes	805 (70.55)	145 (44.62)	0.337 (0.261, 0.434)	<0.0001	0.788 (0.281, 2.206)	0.65
Convulsion previous						
No	743 (65.12)	282 (86.77)	Ref		Ref	
Yes	398 (34.88)	43 (13.23)	0.285 (0.202, 0.403)	<0.0001	0.338 (0.089, 1.290)	0.112
Pallor						
No	867 (76.19)	180 (55.38)	Ref		Ref	
Yes	271 (23.81)	145 (44.62)	2.577 (1.986, 3.345)	<0.0001	1.138 (0.295, 4.390)	0.851
Lymphadenopathy						
No	1119 (98.59)	314 (96.62)	Ref		Ref	
Yes	16 (1.41)	11 (3.38)	2.450 (1.125, 5.336)	0.024	55.320 (5.242, 583.821)	0.001
Sunken eyes						
No	977 (85.85)	237 (72.92)	Ref		Ref	
Yes	161 (14.15)	88 (27.08)	2.253 (1.672, 3.037)	<0.0001	2.511 (0.554, 11.377)	0.232
Respiration deep						
No	801 (70.20)	138 (42.46)	Ref		Ref	

Yes	340 (29.80)	187 (57.54)	3.188 (2.468, 4.118)	<0.0001	0.833 (0.202, 3.427)	0.8
Indrawing						
No	920 (80.63)	184 (56.62)	Ref		Ref	
Yes	221 (19.37)	141 (43.38)	3.186 (2.439, 4.162)	<0.0001	4.342 (0.817, 23.084)	0.085
Flaring						
No	977 (85.63)	203 (62.46)	Ref		Ref	
Yes	164 (14.37)	122 (37.54)	3.577 (2.700, 4.737)	<0.0001	1.369 (0.212, 8.839)	0.741
Irregular respiration						
No	1062 (93.16)	257 (79.08)	Ref		Ref	
Yes	78 (6.84)	68 (20.92)	3.603 (2.531, 5.128)	<0.0001	14.065 (3.076, 64.310)	0.001
Crackles						
No	999 (87.63)	248 (76.31)	Ref		Ref	
Yes	141 (12.37)	77 (23.69)	2.199 (1.610, 3.005)	<0.0001	0.248 (0.025, 2.407)	0.229
Jaundice						
No	1133 (99.30)	317 (97.84)	Ref		Ref	
Yes	8 (0.70)	7 (2.16)	3.125 (1.124, 8.689)	0.029	8.897 (0.133, 594.070)	0.308
Agitation						
No	1043 (91.41)	296 (91.08)	Ref			
Yes	98 (8.59)	29 (8.92)	1.042 (0.675, 1.609)	0.854		
Neck stiffness						
No	1105 (96.84)	307 (94.46)	Ref		Ref	
Yes	36 (3.16)	18 (5.54)	1.798 (1.006, 3.213)	0.048	2.703 (0.720, 10.149)	0.141
Fontanelle bulge						
No	1122 (98.51)	318 (97.85)	Ref			
Yes	17 (1.49)	7 (2.15)	1.453 (0.597, 3.538)	0.411		
Cough						
No	814 (71.34)	201 (61.85)	Ref		Ref	
Yes	327 (28.66)	124 (38.15)	1.540 (1.189, 1.996)	0.001	0.560 (0.121, 2.602)	0.46
Breathing difficulty						

No	860 (75.44)	143 (44.00)	Ref		Ref	
Yes	280 (24.56)	182 (56.00)	3.905 (3.013, 5.060)	<0.0001	0.422 (0.065, 2.729)	0.365
Diarrhoea						
No	941 (82.47)	197 (60.62)	Ref		Ref	
Yes	200 (17.53)	128 (39.38)	3.072 (2.341, 4.032)	<0.0001	2.691 (0.664, 10.897)	0.165
Vomiting						
No	867 (75.99)	195 (60.19)	Ref		Ref	
Yes	274 (24.01)	129 (39.81)	2.101 (1.616, 2.731)	<0.0001	0.595 (0.162, 2.183)	0.434
Skin infection						
No	1108 (97.28)	309 (95.08)	Ref		Ref	
Yes	31 (2.72)	16 (4.92)	1.851 (0.999, 3.426)	0.05	2.962 (0.330, 26.571)	0.332
Sex						
Female	498 (43.65)	151 (46.46)	Ref			
Male	643 (56.35)	174 (53.54)	0.894 (0.693, 1.153)	0.388		
Hiv						
Negative	393 (98.25)	38 (86.36)	Ref		Ref	
Positive	7 (1.75)	6 (13.64)	8.842 (2.823, 27.696)	<0.0001	4.303 (0.526, 35.208)	0.174

Appendix 8: Map of study site

Appendix 9: Do-file

```
***
*Dofile for analysis

*********************************
*********************************
 *ACUTE NON-TRAUMATIC COMA OF UNKNOWN CAUSE*

/*
This do-file is for:
	1. Create analytical file for acute non-traumatic coma of unknown cause
*/

*set directory
clear
cd "C:\Users\eodipo\OneDrive - Kemri Wellcome Trust\Coma\analysis"

**create log file
 log using "log\5_2_20CUC_analysis.log",replace

 set more off

 ***************************
 **Objective 1: Incidence
 ***************************

 *Import person years  data
 use "C:\Users\eodipo\OneDrive - Kemri Wellcome
Trust\Coma\analysis\Data\raw\stratified_PYOs.dta",clear

 *Create required age groups
 tab agecat
 drop if inlist(agecat,0,14)

 recode agecat (0.1664 = 0) (1=1) (3=2) (5=3) (7=4) (9=5) (11=6),gen(age_grp)
 lab def age_grp 0"2-11 mnths" 1 "1-2 yrs" 2 "3-4 yrs" 3 "5-6 yrs" 4 "7-8 yrs" 5 "9-10 yrs" 6 "11-13
yrs"
 lab val age_grp age_grp

 tab age_grp

 **keep required variables
 keep sex year age_grp _Y
 ren _Y person_years

 *save data
 save data/output/person_years, replace
```

```
**collapse by year
collapse (sum) person_years, by(year)

*save data
save data/temp/2002_2018yearly_pop_est,replace


	**********************************************
	**Incidence of aNTC cases among KHDSS residence

	***Yearly Incidence rate of CUC, CM and Meningitis

	 use  data/temp/v3_CUC_def,clear

	 ** group Menengitis and CM into residents and non-residents

	 tab year resident if Meningitis_cat==1
	 tab year resident if CM_cat==1

	*keep residents
	keep if resident==1

	 *collapse dataset
	collapse (sum) CUC_cat Meningitis_cat CM_cat , by(year)

	*merge to person years data
	merge 1:1 year using data/temp/2002_2018yearly_pop_est
	keep if _m==3
	drop _m

	**gen incidence
	gen inc_CUC=round(((CUC_cat/person_years)*100000),.01)
	gen inc_Meng=round(((Meningitis_cat/person_years)*100000),.01)
	gen inc_CM=round(((CM_cat/person_years)*100000),.01)


	**95% CI of the incidence
	gen low_CUC=.
	gen high_CUC=.

	**CUC
forval i=2002/2018{
	preserve
	keep if year== `i'
	ci means inc_CUC, poisson exposure(person_years)
	restore
	scalar low_CUC`i'=r(lb)
	scalar hi_CUC`i'=r(ub)
	}
```

```
forval i=2002/2018{
	replace low_CUC=round((low_CUC`i'*100000),.01) if year== `i'
	replace high_CUC =round((hi_CUC`i'*100000),.01) if year== `i'
	}

	** total incidence
	total(person_years)
	total(CUC_cat)

	di round(((672/1845108)*100000),.01)
	cii means 1845108 672, poisson //33.72; 39.28


	**Meningitis
	gen low_Meng=.
	gen high_Meng=.

	forval i=2002/2018{
	preserve
	keep if year== `i'
	ci means inc_Meng, poisson exposure(person_years)
	restore
	scalar low_Meng`i'=r(lb)
	scalar hi_Meng`i'=r(ub)
	}


forval i=2002/2018{
	replace low_Meng=round((low_Meng`i'*100000),.01) if year== `i'
	replace high_Meng =round((hi_Meng`i'*100000),.01) if year== `i'
	}

	** total incidence
	total(person_years) //1845108
	total(Meningitis_cat) //26

	di round(((26/1845108)*100000),.01) //1.41
	cii means 1845108 26, poisson //0.92; 2.06

	***Cerebral malaria
	gen low_CM=.
	gen high_CM=.

	forval i=2002/2018{
	preserve
	keep if year== `i'
	ci means inc_CM, poisson exposure(person_years)
	restore
```

```
	scalar low_CM`i'=r(lb)
	scalar hi_CM`i'=r(ub)
	}


forval i=2002/2018{
	replace low_CM=round((low_CM`i'*100000),.01) if year== `i'
	replace high_CM =round((hi_CM`i'*100000),.01) if year== `i'
	}

	** total incidence
	total(person_years) //1845108
	total(CM_cat) //758

	di round(((758/1845108)*100000),.01) //41.08
	cii means 1845108 758, poisson //38.21; 44.11


		***Combined graph for incidence of CUC, CM and Meningitis

		// Plotting incidences
	graph twoway ///
	line inc_CUC year, lcolor(green)  || ///
	line inc_Meng year, lcolor(yellow)  || ///
	line inc_CM year,lcolor(blue) , ///
		ytitle("Incidence rate per 100,000 person-years", size(medium))  xtitle("Year")  ///
		ylabel(0(10)115, angle(horizontal) format(%9.0g) labs(vsmall) glwidth(vthin)
glcolor(gs15)) ///
		title("Incidence of aNTC cases among KHDSS Residence") subtitle("2002 - 2018") ///
		xlabel(2002(1)2018, valuelabels labs(vsmall)) ysize(16) xsize(20) graphr(fc(white)) ///
		legend(label(1 {it:CUC}) label(2 {it:Meningitis}) label(3 {it:CM})  size(small) row(2))

		graph export graphs/annual_Coma_incidence.pdf, replace



	*******************************
	**Objective 2: Risk factor analysis
	*******************************
	*********************************
	***********************************
	**Risk factor analysis for mortality cases only

	use data/temp/anaysis_coma_data,clear

	keep if coma_cat!=. //ungrouped excluded

	***Keep only the died cases during admission
	keep if outcome==1
```

```
*****Descriptive for variables considered
	foreach x of varlist weight height head_circ  resp_rate hb_haem heart_rate saturation_oxy 
muac fever_drn{
	bys coma_cat:summ `x'
		}

	foreach x of varlist age_cat temp_cat hypoxia tachypnoea cap_refill_cat oedema_cat 
conv_type convulsion{
	bys coma_cat: tab `x'
		}

	foreach x of varlist cyanosis indrawing resp_deep lymphadenopathy sunken_eyes wheeze 
crackles stridor resp_irregular flaring jaundice skin_infection{
	replace `x' = lower(`x')
		}

	foreach x of varlist dec_skin_turgor fever convulsion_previous temp_gradient pallor 
severe_pallor cyanosis lymphadenopathy sunken_eyes fever pallor resp_deep indrawing {
	bys coma_cat: tab `x'
		}


	foreach x of varlist flaring resp_irregular stridor crackles wheeze  jaundice agitation 
neck_stiffness fontanelle_bulge cough breathing_difficulty diarrhoea vomiting skin_infection  {
	bys coma_cat: tab `x'
		}

	foreach x of varlist pulse_vol conscious_level sex hiv_rslt{
	bys coma_cat: tab `x'
		}

	***Univariate analysis using meningitis as baseline
	foreach x of varlist weight height head_circ  resp_rate hb_haem heart_rate saturation_oxy 
muac fever_drn{
	mlogit coma_cat `x', rrr base(0) vce(cluster fk_person)
		}


	encode dec_skin_turgor,gen(dec1) label(yesno)
	drop dec_skin_turgor
	ren dec1 dec_skin_turgor

	foreach x of varlist dec_skin_turgor fever age_cat temp_cat hypoxia tachypnoea 
cap_refill_cat oedema_cat conv_type convulsion{
	mlogit coma_cat i.`x', rrr base(0) vce(cluster fk_person)
		}
```

```
foreach x of varlist    convulsion_previous temp_gradient pallor severe_pallor cyanosis
lymphadenopathy sunken_eyes resp_deep indrawing{
	replace `x'=lower(`x')
	encode `x',gen(`x'1) label(yesno)
	lab val `x'1 yesno
	drop `x'
	ren `x'1 `x'
	mlogit coma_cat i.`x', rrr base(0) vce(cluster fk_person)
		}


	foreach x of varlist flaring resp_irregular stridor crackles wheeze  jaundice agitation
neck_stiffness fontanelle_bulge cough breathing_difficulty diarrhoea vomiting skin_infection
severe_pallor{
	replace `x'=lower(`x')
	encode `x',gen(`x'1) label(yesno)
	lab val `x'1 yesno
	drop `x'
	ren `x'1 `x'
	mlogit coma_cat i.`x', rrr base(0) vce(cluster fk_person)
		}




	foreach x of varlist pulse_vol conscious_level sex outcome hiv_rslt{
	mlogit coma_cat i.`x', rrr base(0) vce(cluster fk_person)
		}



	************************************
	**********************************
	**Binary logistic regression for CUC outcome

	use data/temp/anaysis_coma_data,clear

	*exclude ungrouped
	keep if coma_cat!=.

	**check outcome
	tab outcome

	*********************
	**CUC
	*********************
	tab coma_cat,nol

	drop if outcome==.
```

```
***********************************
**Univariate analysis for CUC cases
************************************
tab outcome if coma_cat==2

foreach x of varlist weight height head_circ  resp_rate hb_haem heart_rate saturation_oxy
muac fever_drn{
        logit outcome `x' if coma_cat==2, or  vce(cluster fk_person)
        }

foreach x of varlist weight height head_circ  resp_rate hb_haem heart_rate saturation_oxy
muac fever_drn{
        bys outcome:summ `x' if coma_cat==2
        }

        foreach x of varlist weight height head_circ  resp_rate hb_haem heart_rate
saturation_oxy muac fever_drn{
        tabmiss `x' if coma_cat==2
        }

        *********
        foreach x of varlist dec_skin_turgor fever age_cat temp_cat hypoxia tachypnoea
cap_refill_cat oedema_cat conv_type convulsion{
        tabmiss `x' if coma_cat==2
        }

        foreach x of varlist dec_skin_turgor fever age_cat temp_cat hypoxia tachypnoea
cap_refill_cat oedema_cat conv_type convulsion{
        bys outcome:tab `x' if coma_cat==2
        }

br dec_skin_turgor fever
        encode dec_skin_turgor,gen(dec1) label(yesno)
        drop dec_skin_turgor
        ren dec1 dec_skin_turgor

        foreach x of varlist dec_skin_turgor fever age_cat temp_cat hypoxia tachypnoea
cap_refill_cat oedema_cat conv_type convulsion{
        logit outcome i.`x' if coma_cat==2, or vce(cluster fk_person)
        }

        ********
        foreach x of varlist    convulsion_previous temp_gradient pallor severe_pallor
cyanosis lymphadenopathy sunken_eyes resp_deep indrawing{
        replace `x'=lower(`x')
        encode `x',gen(`x'1) label(yesno)
        lab val `x'1 yesno
        drop `x'
        ren `x'1 `x'
        tabmiss `x' if coma_cat==2
```

```
}

foreach x of varlist    convulsion_previous temp_gradient pallor severe_pallor
cyanosis lymphadenopathy sunken_eyes resp_deep indrawing{
bys outcome:tab `x' if coma_cat==2
}

foreach x of varlist    convulsion_previous temp_gradient pallor severe_pallor
cyanosis lymphadenopathy sunken_eyes resp_deep indrawing{
logit outcome i.`x' if coma_cat==2, or vce(cluster fk_person)
}

***********
foreach x of varlist flaring resp_irregular stridor crackles wheeze  jaundice agitation
neck_stiffness fontanelle_bulge cough breathing_difficulty diarrhoea vomiting skin_infection {
replace `x'=lower(`x')
encode `x',gen(`x'1) label(yesno)
lab val `x'1 yesno
drop `x'
ren `x'1 `x'
tabmiss `x' if coma_cat==2
}

foreach x of varlist flaring resp_irregular stridor crackles wheeze  jaundice agitation
neck_stiffness fontanelle_bulge cough breathing_difficulty diarrhoea vomiting skin_infection {
bys outcome:tab `x' if coma_cat==2
}

foreach x of varlist flaring resp_irregular stridor crackles wheeze  jaundice agitation
neck_stiffness fontanelle_bulge cough breathing_difficulty diarrhoea vomiting skin_infection {
logit outcome i.`x' if coma_cat==2, or vce(cluster fk_person)
}

**************
foreach x of varlist pulse_vol conscious_level sex hiv_rslt{
tabmiss `x' if coma_cat==2
}

foreach x of varlist pulse_vol conscious_level sex hiv_rslt{
bys outcome:tab `x' if coma_cat==2
}

foreach x of varlist pulse_vol conscious_level sex hiv_rslt{
logit outcome i.`x' if coma_cat==2, or vce(cluster fk_person)
}


**************************
*****Multivariable analysis
```

```
        ***************************
        logit outcome weight height head_circ  resp_rate muac i.dec_skin_turgor i.fever i.age_cat  i.hypoxia i.tachypnoea i.cap_refill_cat ///
        i.oedema_cat i.convulsion  i.convulsion_previous i.temp_gradient i.pallor i.lymphadenopathy i.sunken_eyes ///
        i.resp_deep i.indrawing i.flaring i.resp_irregular i.crackles   i.jaundice i.neck_stiffness ///
        i.cough i.breathing_difficulty i.diarrhoea i.vomiting i.skin_infection  i.hiv_rslt if coma_cat==2, or vce(cluster fk_person)

    est store A

    estat ic

    logit outcome weight height head_circ  resp_rate muac i.dec_skin_turgor i.fever i.age_cat i.hypoxia i.tachypnoea i.cap_refill_cat ///
        i.oedema_cat i.convulsion i.convulsion_previous  i.pallor  i.lymphadenopathy i.sunken_eyes ///
        i.resp_deep i.indrawing i.flaring i.resp_irregular i.crackles   i.jaundice i.neck_stiffness ///
        i.cough i.breathing_difficulty i.diarrhoea i.vomiting i.skin_infection  i.hiv_rslt if coma_cat==2, or vce(cluster fk_person)

    estat ic

    **********************************
    *Objective 3: Time series analysis
    **********************************
    ****load CUC data
    use data/temp/anaysis_coma_data,clear

    *create year month variable
    g dm=mofd(doa)
    format dm %tm

    ren dm yr_mon

    *collapse data
    collapse (sum) Meningitis_cat CM_cat CUC_cat ungrouped, by(yr_mon)
    sort yr_mon

    gen tt_coma = Meningitis_cat + CM_cat + CUC_cat + ungrouped

    *calculate proportions
    gen meng_prop = round((Meningitis_cat/tt_coma)*100, .01)
    gen cm_prop = round((CM_cat/tt_coma)*100, .01)
    gen cuc_prop = round((CUC_cat/tt_coma)*100, .01)


    **set time series data
```

```
sort yr_mon
tsset yr_mon


***test for stationarity assusmption
dfuller CUC_cat  , regress trend

**Correlogram ACF and PACF
corrgram CUC_cat //peaks (5,12,14,17)

***trying to pick the seasonality
reg d.CUC_cat l.CUC_cat
predict  res1 ,r

**check if the peaks you selected above are the same here
corrgram res1

***confirmas the significant of the seasonality
wntestq res1


***a correlogram (a graph of autocorrelations) with pointwise confidence intervals that is based on Bartlett's formula
ac CUC_cat

pac CUC_cat

****
arima CUC_cat, arima(1,0,2)
arima CUC_cat,  arima(1,0,2) noconstant
estat ic
predict arima12

*****fit predict and fitted
tsline l1.CUC_cat arima12 , title("", size(large)) subtitle("",size(medium))  ytitle("Count of CUC" ,size(vlarge)) xtitle("Yearly months", size(vlarge)) ///
graphregion(color(white) lcolor(white)) xsize(20) ylabel(,labsize(vvlarge)) xlabel(,labsize(vvlarge)) lwidth(vthick)  legend(on)  plotregion(lcol(black) lwidth(thin)) ///
saving("figures\mnths_count_predicted",replace)


*****************
**Mortality trend
use data/temp/anaysis_coma_data,clear


keep if outcome ==1

*collapse data
collapse (sum) Meningitis_cat CM_cat CUC_cat ungrouped, by(year)
```

```
gen tt_coma = Meningitis_cat + CM_cat + CUC_cat+ungrouped

**obtain proportions
gen meng_prop = round((Meningitis_cat/tt_coma)*100, .01)
gen cm_prop = round((CM_cat/tt_coma)*100, .01)
gen cuc_prop = round((CUC_cat/tt_coma)*100, .01)
gen ungrp_prop = round((ungrouped/tt_coma)*100, .01)

**Plot graph
graph twoway ///
line cuc_prop year, lcolor(green)  || ///
line meng_prop year, lcolor(yellow)  || ///
line cm_prop year, lcolor(blue)  || ///
line ungrp_prop year, lcolor(orange) , ///
ytitle("Proportion", size(medium))  xtitle("Year")  ///
ylabel(0(10)100, angle(horizontal) format(%9.0g) labs(vsmall) glwidth(vthin) glcolor(gs15))
///
title("Annual aNTC Proportion of Deaths") subtitle("2002 - 2018") ///
xlabel(2002(1)2018, valuelabels labs(vsmall)) ysize(16) xsize(20) graphr(fc(white)) ///
legend(label(1 {it:CUC}) label(2 {it:Meningitis}) label(3 {it:CM}) label(4 {it:Ungrouped})
size(small) row(2))


log close
```