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Changing trends in incidence and aetiology of childhood acute non-traumatic coma over a period of changing malaria transmission in rural coastal Kenya: a retrospective analysis

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ABSTRACT

Objectives: Recent changes in malaria transmission have likely altered the aetiology and outcome of childhood coma in sub-Saharan Africa. The authors conducted this study to examine change in incidence, aetiology, clinical presentation, mortality and risk factors for death in childhood non-traumatic coma over a 6-year period.

Design: Retrospective analysis of prospectively collected data.

Setting: Secondary level health facility: Kilifi, Coast, Kenya.

Participants: Children aged 9 months to 13 years admitted with acute non-traumatic coma (Blantyre Coma Score ≤2) between January 2004 and December 2009 to Kilifi District Hospital, Kenya. Exclusion criteria: delayed development, epilepsy and sickle cell disease.

Results: During the study period, 665 children (median age 32 (IQR 20–46) months; 46% were girls) were admitted in coma. The incidence of childhood coma declined from 93/100 000 children in 2004 to 44/100 000 children in 2009. There was a 64% overall drop in annual malaria-positive coma admissions and a 272% overall increase in annual admissions with encephalopathies of undetermined cause over the study period. There was no change in case death of coma. Vomiting, breathing difficulties, bradycardia, profound coma (Blantyre Coma Score=0), bacteraemia and clinical signs of meningitis were associated with increased risk of death. Seizures within 24 h prior to admission, and malaria parasitaemia, were independently associated with survival, unchanging during the study period.

Conclusion: The decline in the incidence and number of admissions of childhood acute non-traumatic coma is due to decreased malaria transmission. The relative and absolute increase in admissions of encephalopathy of undetermined aetiology could represent aetiologies previously masked by malaria or new aetiologies.

ARTICLE SUMMARY

Article focus

- This study examines change in incidence, aetiology, clinical presentation, mortality and risk factors for death in childhood acute non-traumatic coma over a 6-year period of documented change in malaria transmission in rural coastal Kenya.

Key messages

- There is an overall decline in childhood coma presentation over the study period, with a significant drop in malaria-positive coma admissions.
- There is relative and absolute increase in coma admissions of undetermined aetiology.
- There is an urgent need to examine for the role of viruses, metabolic derangements, vascular pathologies and other conditions in the aetiology of childhood non-traumatic coma.

Strengths and limitations of this study

- The study is based on prospectively collected data in a setting where recommended standard clinical care is consistent and for which the catchment area is well delineated.
- A number of children with acute coma likely die before arrival in hospital, and a few others are seen in a smaller hospital, which refers most of their comatose patients to the hospital in the study. Thus, the incidence figures are minimum incidences, likely an underestimation of the actual incidence.

INTRODUCTION

Acute non-traumatic coma is a frequently encountered paediatric presentation in sub-Saharan Africa (SSA). Often, it is attributed to cerebral malaria (CM), acute bacterial meningitis (ABM) and viral encephalitides, conditions that are associated with high

mortality and significant risk of neurological sequalae.[1 2] In malaria-endemic areas, misdiagnosis and comorbidity complicate the accurate diagnosis of coma even where diagnostic practices are optimal.[3 4] Thus, the common practice is to provide empirical treatment with antimalarials and antimicrobials.[5] However, the risks of such practice are undertreatment of potentially life-threatening conditions, incorrect estimation of disease burden and misunderstanding of the pathophysiology of individual conditions. There is also the risk of development of resistance to first-line antimicrobials and antimalarials.

In recent years, we have observed a significant reduction in malaria transmission and in the absolute incidence of malarial disease presenting to hospitals on the Kenyan coast.[6] This has been accompanied by reduction of up to 75% in severe disease and deaths from malaria. We expect a proportionate reduction in the incidence of CM and overall, of childhood coma presentations. Such an epidemiological transition provides an opportunity to re-examine the role of malaria in the aetiology of coma and define new priorities in coma research in SSA. It also raises questions about public health strategies and diagnostic and treatment protocols for coma in African children.

In this study, we examine the incidence, aetiology, clinical characteristics, mortality and risk factors for death in children presenting with coma to a district hospital on the Kenyan coast over a period of 6 years of documented change in malaria transmission.

METHODS

Study setting

Kilifi District Hospital (KDH) is centrally placed within Kilifi District, a malaria-endemic administrative region in rural coastal Kenya, and serves as a first referral centre for patients requiring hospital admission. It has a 50-bed capacity paediatric ward supported by a seven-bed high dependency unit to which children with coma are admitted. Approximately 5000 children (≤13 years) are admitted to the hospital annually; about 15% are severely or critically ill and are initially managed in the high dependency unit. The hospital and the region have no paediatric intensive care unit. Two-thirds of the population in Kilifi District live in 14 locations surrounding KDH, from which 80% of paediatric admissions come. These 14 locations have been incorporated into the Kilifi Demographic and Health Surveillance Site (KDHSS). There is one smaller hospital outside the KDHSS, St Lukes (figure 2), which admits patients but often refers those with coma to KDH.

Study population

We analysed prospectively collected data on children aged between 9 months and 13 years who presented with acute coma (Blantyre Coma Score (BCS) <2 persisting for longer than 30 min after correction of hypoglycaemia and first-line antiepileptic drug treatment).[7] The BCS is a simple score of coma status, similarly based on assessment of motor, verbal and eye opening as the modified Glasgow coma scale, but preferred in malaria-endemic areas because of its simplicity and better interobserver agreement among health workers in this setting.[7] Children younger than 9 months were not considered because at their developmental stage they cannot localise painful stimuli, a key criterion in our assessment of coma. Children with previous epilepsy or significant developmental delay were excluded. The period of the study was January 2004 to December 2009. This study was approved by the Kenya Medical Research Institute Ethics Review Board (SCC 1249).

Standard care

At admission, children received emergency care, including correction of hypoxaemia, shock, hypoglycaemia, severe electrolyte abnormalities and anaemia, based on standard guidelines.[8] Initial laboratory investigations included blood glucose, full blood count, creatinine and electrolyte levels, malaria blood slide and blood culture. Lumbar puncture was performed when the child's respiratory and cardiovascular functions were stable and there were no brainstem signs. The cerebrospinal fluid (CSF) was examined for evidence of infection. CM was identified using the WHO definition; coma in a child, defined as unable to localise a painful stimulus, with asexual malaria parasitaemia in the absence of an alternative explanation for cause of illness.[9] A diagnosis of ABM was considered when bacteria were detected on CSF culture, gram stain or bacterial antigen testing or when there was a CSF leucocyte count of at least 10/μl and the blood: CSF glucose ratio was <0.67.[10] Children with no history of trauma and no indication of CM, ABM or bacteraemia were considered to have an encephalopathy of undetermined cause.[11] The hospital had no capacity to ascertain a diagnosis of viral encephalitis or carry out imaging studies using CT or MRI. An opt-out policy for routine HIV serology testing at admission was implemented between February 2006 and December 2008. Prior to this, HIV serology testing was done at the discretion of the attending clinician. The records for the year 2009 were not available to us. All children were initially treated with parenteral first-line antimicrobials and antimalarials until otherwise guided by the results of the initial three malaria blood slides taken 8 h apart, blood, urine or CSF culture, and CSF microscopy and biochemistry results. Acyclovir was not available. Other aspects of supportive care included treatment of seizures and administration of maintenance fluids.

Data analysis

Individual clinical data were directly entered in a FileMaker 5.5 database at admission. We analysed the data using Intercooled Stata V.11.1 (Stata Corp LP). We calculated the minimum annual incidence of coma for children aged 9 months to 13 years by dividing the annual number of children admitted in coma from the KDHSS by the midyear population of this age group

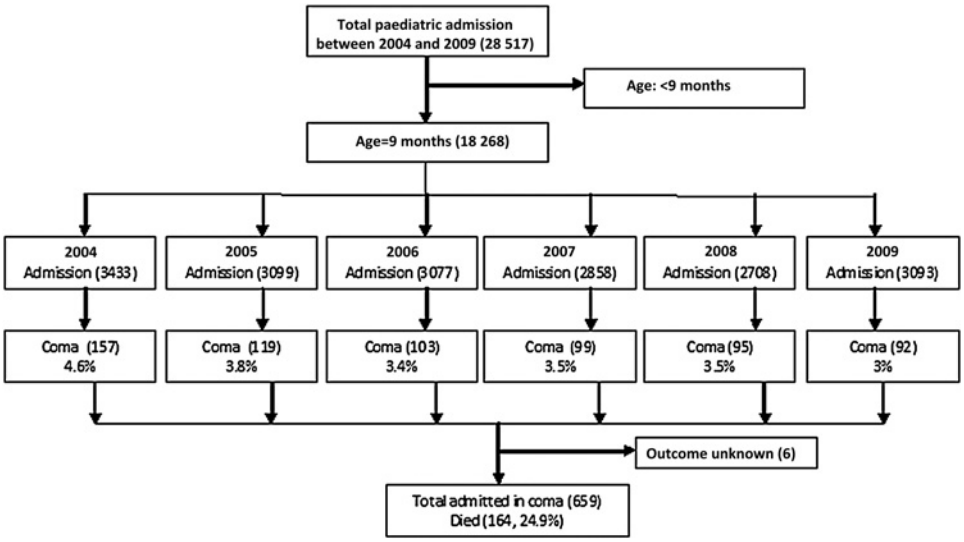

Figure 1 Flow diagram showing the children admitted to Kilifi District Hospital in Kenya between 1 January 2004 and 31 December 2009 (N=28 517).

from the same area.[6] We investigated the risk of admission with coma among children in the KDHSS by Euclidian distance from the hospital. Distance was measured directly from the residence of patients to the hospital and categorised into quintiles. We used a non-parametric score test to assess the trends in the risk of admission and case death by distance from the hospital. We described the univariable association between each candidate risk factor and death using ORs and 95% CIs using logistic regression. We included all the variables in the univariable analysis in a multivariable logistic regression model using a forward stepwise method, in descending order of the magnitude of association with death. We compared the model fit using a likelihood ratio test and used the conventional significance level of 5% for retention of the risk factors in the final model. A likelihood ratio test for interaction was carried out to assess if the risk factors for death varied by aetiology or calendar year. We also carried out a secondary analysis to define the possible causes of encephalopathies with undetermined cause. We explored baseline differences between encephalopathies of undetermined aetiology and those with invasive bacterial disease or malaria using χ^2 test and Fisher's exact test for categorical variables, and unpaired t test or Wilcoxon rank-sum test for continuous variables.

Table 1 Annual incidence and case death of childhood coma between 2004 and 2009

Year	Mean incidence/ 100 000 children	95% CI	Case death
2004	93	74 to 115	20.4
2005	54	40 to 71	26.7
2006	63	48 to 81	22.3
2007	55	41 to 71	34.0
2008	43	31 to 57	23.2
2009	44	32 to 59	25.3

RESULTS

Between January 2004 and December 2009, 665 children with coma fulfilling our study criteria were admitted to the KDH (figure 1). The median age was 32 (IQR 20–46) months, and 306 (46%) were girls. The baseline characteristics are summarised in supplementary table 1. Over the study period, there was a 53% decrease in the annual minimum incidence of coma, from 93/100 000 children in 2004 to 44/100 000 children in 2009 (table 1). The risk of being admitted with coma increased with distance from the hospital (χ^2 score test for trend of odds; $p<0.01$) (figure 2 and supplementary figure 1).

Aetiology

During the period of observation, 393 (59%) children had malaria parasitaemia, three of whom had concurrent invasive bacterial infection (one ABM and sepsis, and two sepsis), while 27 had CSF biochemistry and white cell count compatible with ABM (supplementary figure 1). In total, 27 (4%) children had culture proven invasive bacterial infection (supplementary table 2); six of them had concurrent blood and CSF isolates and were the only children with culture proven ABM (all pneumococcal meningitis). Thirty-seven children (including the 27 with concurrent malaria parasitaemia) had CSF features of ABM in the absence of bacterial isolates; thus in total, 43 children were considered to have ABM. Two hundred and thirty-eight children (36%) had encephalopathies of undetermined cause (supplementary figure 2). Ninety children (14%) did not have a history of fever at admission, including 60 (25%) with encephalopathies of undetermined aetiology. Two hundred and twenty-two (33%) children were tested for HIV; 12 (5% of those tested) were found to have positive serology for HIV and three had discordant results (inconsistency in the test results by the two different HIV antibody test kits used). The proportions of children tested were not different across the different aetiologies (CM 30%, ABM 40%, bacteraemia 38% and encephalopathies of undetermined

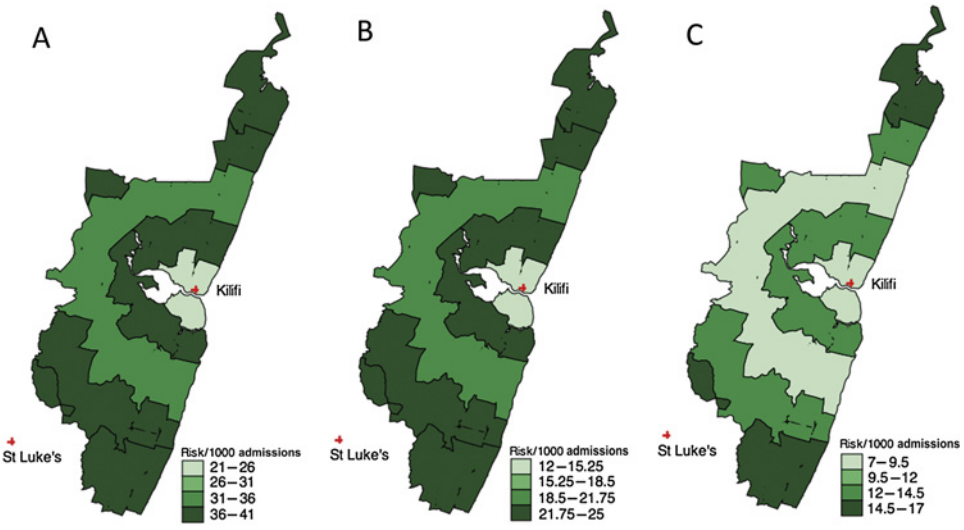

Figure 2 Choropleth maps comparing coma presentation with distance from the hospital at the Kilifi demographic surveillance site. Distance from the hospital is divided into equal quintiles. Map A represents a plot of risk of all-cause coma admissions among all admissions of similar age group with distance from the hospital and shows a significant overall trend of increasing risk with distance (score test for trend, p<0.01). Map B represents risk of malaria-positive coma admissions, and map C represents risk of encephalopathies of undetermined aetiology among children presenting with coma; both demonstrate overall increased risk with increasing distance from the hospital (score test for trend, p<0.01 for the three categories). In all the maps, the second distance quintile is characterised by unexpected greater risk than the third distance quintile, thus the rising risk with distance is interrupted.

aetiology 36%). Between 2004 and 2009, there was a significant decrease in the overall coma admissions, from 4.6% of all admissions between the age of 9 months and 13 years in 2004 to 3.0% in 2009 (χ^2 score test for trend of odds; p<0.01) (figures 1 and 3). There was a 64% decline in the proportion of comatose children with malaria parasitaemia, from 76% (n=119) of coma admissions in 2004 to a low of 27% (n=26) in 2009 (χ^2 score test for trend of odds; p<0.01) (figure 3). The prevalence of confirmed invasive bacterial disease and ABM in the coma admissions also decreased significantly over the same duration (χ^2 score test for trend of odds; p<0.01) (figure 3). However, there was a significant rise in the both the absolute numbers and relative proportion of children with encephalopathies of undetermined cause, from 21% (n=33) of coma admissions in 2004 to 72% (n=66) in 2009 (figure 3).

Mortality

During the period of observation, 164 (25%) children died. Sixty-three (38%) had malaria parasitaemia, 23 (14%) had confirmed invasive bacteraemia and 78 (48%) had encephalopathy of undetermined aetiology. Overall, the case death was 33% for encephalopathy of undetermined aetiology, 16% for malaria, 35% for meningitis (50% for culture proven bacterial meningitis) and 78% for all cases of bacteraemia. Twenty-seven per cent of all deaths occurred on the day of admission and 53% died within the first 48 h of admission. The case death for coma fluctuated between 2004 and 2009, but we did not observe any consistent trend (table 1) (score test for trend of odds, p=0.34). There was no evidence that the case death for each aetiological category, even for encephalopathies of undetermined aetiology, changed from year to year, or consistently with distance from the hospital (supplementary figure 3).

There was significant decline in the incidence of non-traumatic coma over the study period (score test for trends of odd, p<0.01). There was no significant change in the case death of non-traumatic coma over the same period (score test for trends of odd, p=0.34).

On initial univariable analysis, many clinical factors in the admission history and examination (supplementary table 3) were associated with greater risk of death. However, notably, severe anaemia (haemoglobin <500 g/l) at admission was not associated with mortality. On multivariable analysis, vomiting, breathing difficulties (tachypnoea, intercostal indrawing and need for oxygen) as assessed by the clinician at admission, bradycardia, deep coma (BCS=0), bacteraemia and clinical signs of meningitis (stiff neck or bulging fontanelle) were independently associated with increased risk of death (table 2). A history of seizures within 24 h prior to admission and malaria parasitaemia were independently associated with reduced risk of death (OR 0.3, 95% CI 0.2 to 0.5 (p<0.01) and OR 0.5, 95% CI 0.3 to 0.8 (p<0.01), respectively). There was no evidence that the risk factors for death varied with year (likelihood ratio test, p>0.10).

Clinical presentation of encephalopathies of undetermined aetiology

Children with encephalopathies of undetermined aetiology were more likely to present with diarrhoea, hypoxia, signs of severe pneumonia, severe dehydration, be more deeply comatose at admission and have admission hypokalaemia compared with those in whom an organism had been identified (supplementary table 4). Their mortality was also higher. Conversely, they were less likely to present with a history of fever, seizures within 24 h prior to admission and severe anaemia.

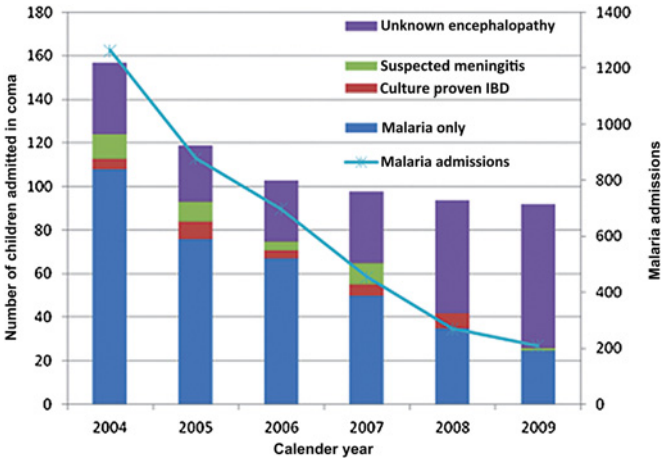

Figure 3 Trends in aetiology of paediatric coma admissions. There is a decrease in the number and proportion of children presenting with malaria parasitaemia and an absolute and proportionate increase in the number of those presenting with unknown encephalopathies. Overall malaria admission is significantly reduced over the study period. IBD, invasive bacterial disease.

DISCUSSION

Acute coma is a common presentation of childhood illnesses in malaria-endemic areas of SSA. Usually, it is associated with malaria parasitaemia, but it can also be due to ABM, viral encephalitides, cerebrovascular abnormalities and metabolic derangements. In this study, we demonstrate change in the aetiological profile of coma with changing malaria transmission in a rural malaria-endemic area in SSA. Thus, by the end of the study period, we had observed a 64% decrease in childhood coma admissions with malaria parasitaemia. We also noted a significant increase in the relative proportions and in the absolute numbers of children with encephalopathies of undetermined aetiology. Overall, there was a decline in childhood coma presentation over this period, indicating the prominent role malaria had played in the causation of coma. By the nature of the analysis, the minimum annual incidence of coma is likely to be a significant underestimate of the actual incidence. In spite of this, the lowest minimum annual incidence of coma observed over the study period, 44/100 000 children in 2009, is markedly greater than that observed in a defined region in the UK; 30.8/100 000 children in a study that included children with epilepsy, intoxication and complications of congenital abnormalities and malignant diseases.[12] This indicates the greater burden of non-traumatic coma in this setting, likely attributable to infectious diseases, and the need to improve on the care and interventions for this group of children. Admissions with coma from within the KHDSS increased with distance from the hospital, perhaps indicating the influence of health facility access on disease severity. Thus, individuals living nearer the hospital were more likely to access the hospital earlier in their illnesses before deteriorating into coma. The first quintile area also represents a relatively well-off population in an urban set-up who may have other options for accessing healthcare. Notwithstanding the demographic peculiarity of the first quintile area, the second layer represents the group that would be in the position of maximal utilisation of the hospital and thus, higher ascertainment, a factor that is likely to undergo distance-related attenuation. This could explain why we observe an unexpectedly greater incidence of childhood coma and higher case death than the third quintile area. It is possible that there may be other uninvestigated epidemiological factors at play to further explain this.

Although malaria parasitaemia was associated with better outcome, the decline in the relative and absolute numbers of comatose children with malaria parasitaemia was not associated with a change in the case death of coma over the study period. There was an accompanying increase in the absolute numbers and proportions of children with encephalopathies of undetermined cause over the same period. Thus, it could be that the decline in malaria transmission revealed undetermined non-malarial aetiology in a proportion of children who had coincidental malaria parasitaemia. Indeed, an autopsy study in Malawi revealed that 23% of the children diagnosed to have CM had actually died of other causes such as Reye-like syndrome and ruptured arteriovenous malformation.[4] In another study at KDH, we found that 9% of the children diagnosed to have CM were found to have evidence of herpes simplex 1 infection in their CSF.[13] Thus, a significant proportion of comatose children may actually suffer from CNS viral infections, vascular and metabolic syndromes and other conditions that are masked by malaria parasitaemia. It is more likely that infectious aetiologies would be the cause of such significant occurrence of acute non-traumatic encephalopathy of undetermined aetiology among individuals who have previously been well and have had normal growth and development.

Children with coma of undetermined aetiology were more likely to have a history of diarrhoea, severe dehydration and features of severe pneumonia, perhaps

Table 2 Multivariable analysis to determine predictors for death in children admitted in coma in Kilifi district hospital in Kenya between 2004 and 2009 (N=665)

Characteristic	OR (95% CIs)	p Value
Difficulty breathing	2.2 (1.3 to 3.5)	0.001
Bradycardia	4.3 (1.5 to 12.6)	0.008
Deep coma (BCS=0)	1.6 (1.2 to 2.1)	0.002
Vomiting	2.1 (1.3 to 3.4)	0.002
Bacteraemia	14.9 (4.9 to 45.3)	<0.001
Clinical signs of meningitis†	3.9 (1.3 to 11.6)	0.013
Seizures within 24 h*	0.3 (0.2 to 0.5)	<0.001
Malaria parasitaemia	0.5 (0.3 to 0.8)	0.007

*Seizures within 24 h prior to admission.
†Stiff neck or bulging fontanelle.
BCS, Blantyre Coma Score.

suggesting gastrointestinal and respiratory foci of initial infection. These clinical features are not specific to a particular aetiology but may guide diagnostic tests, clinical monitoring and supportive interventions to improve outcome. Children with coma of undetermined aetiology were less likely to have a history of fever at presentation compared with those with determined aetiology. Even so, a relatively small proportion (26% of children with encephalopathy of undetermined aetiology) did not have fever. Fever in children presenting with coma is usually intermittent, and absence of raised temperature or a subjective history of fever at admission does not necessarily mean that there was not any occurrence of fever during the illness. Our data do not include serial temperature measurements after admission, but even if we had, it is possible that routine intervention with antipyretics would have altered perception or observation of fever during the period of admission. Children with coma of undetermined aetiology were less likely to present with seizures at admission compared with those with determined aetiology. Falciparum malaria is known to be epileptogenic, and this could explain why children with coma of determined aetiology, for which CM formed a great proportion, were more likely to have seizures compared with those with coma of undetermined aetiology. Initial studies suggested specificity of malarial retinopathy in determining a diagnosis of CM.[4 14] However, recent studies indicating presence of malarial retinopathy in non-cerebral severe malaria indicate that this finding is not specific.[15] Determining the actual sensitivity and specificity of malarial retinopathy is difficult because the gold standard is brain involvement as indicated at autopsy or biopsy, which is not practical. Indirect funduscopy to observe for malarial retinopathy is still not routine and was not consistently performed from the outset in our study. We demonstrate an increasing number and proportion of children with no malaria parasitaemia, for whom indirect funduscopy would not have further clarified the absence of CM. Children with encephalopathies of undetermined cause were more likely to die than those with a definite diagnosis, probably due to increased virulence or undertreatment of an unisolated organism or lack of treatment for other undiagnosed conditions. It is crucial that we understand the aetiology of these encephalopathies to inform preventive, diagnostic and treatment practice for better outcome.

Bacteraemia and a diagnosis of meningitis were associated with an increased risk of death, thus highlighting the need for early parenteral antibiotics in coma until bacterial infection is excluded. Introduction of the *Haemophilus influenza* B conjugate vaccine in this set-up has been associated with a significant reduction in *Haemophilus influenza* B meningitis.[16 17] It is expected that the recent launch of universal pneumococcal conjugate vaccine in the region will similarly result in significant reduction in cases of ABM.[18 19] Vaccine interventions will likely alter aetiology and outcome of coma in SSA.

History of seizures at admission was associated with reduced risk of death. Simple short seizures commonly occur in neurologically intact children with fever and may reduce time to admission in encephalopathy, hence the association with survival. The association between seizures and adverse outcome may be specific to morbidity or related to recurrence or persistence and refractoriness to anti-epileptic drugs (AED) treatment. None of the observed risk factors for death were altered with time in spite of the apparent change in aetiology over the study period. There is therefore a possibility that the actual aetiology of coma did not significantly change over the study period.

The change in malaria transmission in rural coastal Kenya is likely due to a number of interventions. Increased bed net use and widespread introduction of effective artemisinin-based combination antimalarial drugs are some of the specific interventions against malaria that may have impacted on malaria transmision.[6] Other factors such as economic development, better housing and environmental management of mosquito breeding sites may also have contributed to this decline.

Our study had some limitations. An opt-out policy for HIV serology testing at admission was implemented between February 2006 and December 2008. Thus, HIV testing was not consistently performed over the study period. Only 12 (5.4%) of those tested were found to be HIV positive, and there was no difference in diagnosis or outcome between those who were tested for HIV and those who were not. There is a smaller hospital, which is located just outside the KDHSS, with limited paediatric inpatient capacity and refers the majority of its coma admissions to our hospital. We cannot ascertain the number of children who died on their way to hospital or at home without seeking medical care. Thus, our incidence data are minimum incidence and likely an underestimate of the actual incidence.

Studies elucidating the incidence and aetiology of childhood coma and the related outcome in Africa are virtually non-existent. We believe that there is an urgent need to prospectively examine for the role of viruses, vascular pathologies, coagulation problems and metabolic derangements, in the aetiology of coma in SSA. It will also be important to investigate for affordable and practical diagnostic methods for the diagnosis of bacterial and viral infections and conduct trials to determine appropriate empirical combinations for coma treatment considering the change in malaria transmission. Serological tests presented in the form of rapid diagnostic tests may be part of the solution in resource-poor SSA.

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Contributors SG conceived the study, performed data analysis and drafted the manuscript. NT helped in designing the study, performed data analysis and assisted in interpretation of the results and in editing the manuscript. RI, MN, MB, CN and FK assisted with the study design, data analysis and interpretation of the results and drafting of the manuscript. SG had access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests None.

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