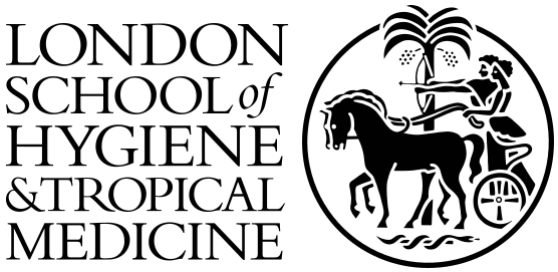

The Neurological Sequelae of Cerebral Malaria in Children and Adults in Uganda

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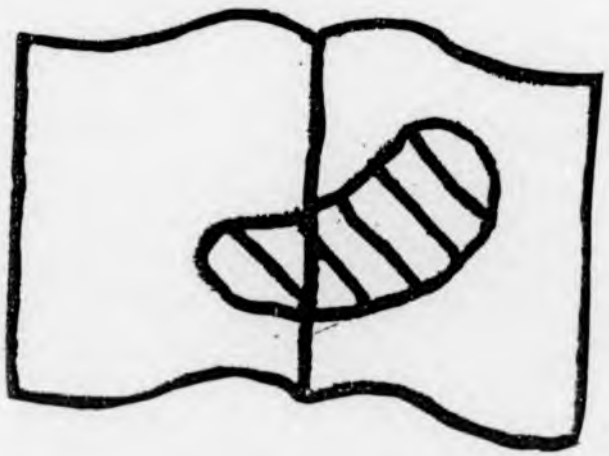

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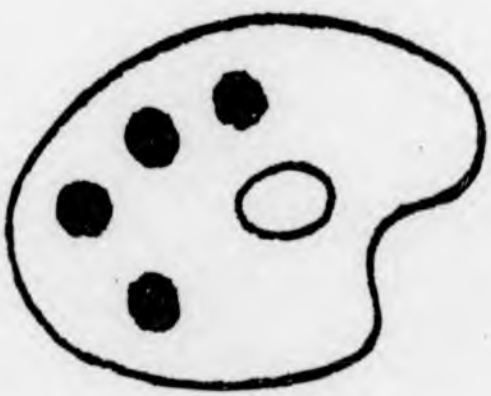

ABSTRACT

Cerebral malaria is one of the severe manifestations of falciparum malaria. It has a high fatality rate and survivors are at risk of a variety of neurological sequelae. The characteristics and determinants of neurological sequelae have been extensively studied in children aged under five years. Survivors who are over five years are known to develop sequelae and indications are that they may be at higher risk. This study set out to identify the sequelae that are present in children and adults in Uganda and to examine if there were differences in the occurrence, natural history and determinants of deficits. The study employed a multi-centre design using study hospitals that were located in malaria epidemic-prone areas in Uganda so as to enrol patients with a wider age distribution than would have been the case in malaria endemic sites.

One hundred patients were enrolled between 1 January 2002 and 31st July 2003. The proportion of cerebral malaria among malaria admissions was 1.9% (72/3789) in children and 1.8% (28/1592) in adults admitted to the study hospitals. The case fatality ratio was low, 10%, and young children under five years of age at the time of admission had the highest mortality. Thirty-five survivors were detected to have neurological sequelae of which 63% were of the motor-sensory kind (22 survivors), 20% of the cognitive kind (7 survivors) and 17% had both kinds (6 survivors). The proportion of survivors with neurological sequelae was slightly higher in adults, 42% (11/26) than children, 38% (24/64). The more striking age difference was the frequency of sequelae among survivors aged under five, 28% (11/40), and those aged 5 to 9 years, 54% (13/24). Deficits were present in twenty-three survivors at discharge (motor-sensory sequelae only) and nineteen survivors that attended review visits (motor-sensory and cognitive sequelae). Deficits involving muscle tone (detected in 18 survivors), tendon reflexes (14 survivors) and muscle power (12 survivors) were the commonest at discharge, occurring in combination. Impaired muscle strength (5 cases) was the commonest motor-sensory sequela detected during follow-up. The commonest cognitive deficit either reported by mothers of survivors or detected by the cognitive tool was memory impairment which was found in 10 survivors. The natural history of sequelae did not differ between children and adults.

Mortality was independently associated with quinine use within 48 hours prior to admission, seizures while on the ward and parasite count on admission. Quinine use prior to admission, duration of coma, duration with a history of fever plus days in hospital with a high temperature and splenomegaly were independently associated with early-onset deficits. The detection and development of late-onset deficits was associated with duration of elevated body temperature, duration taken to control seizures and the presence of neurological deficits at discharge. It was not possible to examine the determinants for the outcomes in children and adults separately.

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This work had a beginning, middle and an end stage. At each stage, a considerable number of people, groups and institutions contributed towards the ultimate goal of a successful end. The journey was a tedious and long one. It would be an impossible task to name everyone I should and therefore those who are not acknowledged herein are no less important than those mentioned.

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GLOSSARY OF TERMS

Term	Meaning
Younger children	Children aged between 1 and 4 years at the time of admission
Older children	Children aged between 5 and 9 years at the time of admission
Adults	Persons aged 10 years and above
Early-onset neurological deficits	Features of neurological dysfunction that are detected at time of discharge and attributable to cerebral malaria
Late-onset neurological deficits	Features of neurological dysfunction that are detected in the period after discharge and attributable to cerebral malaria

LIST OF ABBREVIATIONS

Abbreviation	Meaning
AIDS	Acquired Immunodeficiency Syndrome
An.	*Anopheles*
ATP	Adenosine triphosphate
BCS	Blantyre Coma Scale
CFR	Case fatality ratio
CI	Confidence intervals
CM	Cerebral malaria
CNS	Central Nervous System
conc	Concentration
CRF	Case record form
CS	Cognitive neurological sequelae
CSF	Cerebrospinal fluid
DCM	Definite case of cerebral malaria
DDHS	Director of the District Health Service
DHS	District Health Service
EANMAT	East African Network for Monitoring Antimalarial Treatment
EEG	Electroencephalogram
ELISA	Enzyme-Linked Immunosorbent Assay
E-selectin	Endothelial leukocyte adhesion molecule-1
ESR	Erythrocyte Sedimentation rate
GCS	Glasgow Coma Score
GOU	Government of Uganda
Hb	Haemoglobin
Hct	Haematocrit
HIV	Human Immunodeficiency Virus
hpf	High power field
HR	Hazard ratio
hr/s	Hour/s
ICAM-1	Intracellular adhesion molecule-1

Continued overleaf

Abbreviation	Meaning
IR	Incidence rate
IRR	Incidence rate ratio
IV	Intravenous
kg	Kilogram
km	Kilometre
LGVC	Language and verbal comprehension instructions
LGVCTotal	Total score for Language and verbal comprehension instructions
m	metre
MEM	Memory instructions
MEMtotal	Total score for Memory instructions
mg	Milligram
mg/kg	Milligrams per kilogram
mm	Millimetre
mmHg	Millimetres of mercury
mmol	Millimoles
MO	Medical Officer
MOH	Ministry of Health, Uganda
MP	Malaria parasite
MS	Motor-sensory neurological sequelae
mth/s	Month/s
NA	Not applicable
NO	Nitric oxide
No.	Number
NPRBCS	Non-parasitised red blood cells
NS	Not specified
°C	Degrees Celsius
OR	Odds ratio

Continued overleaf

Abbreviation	Meaning
P.	*Plasmodium*
PCM	Probable case of cerebral malaria
PI	Principal Investigator
PRBCS	Parasitised red blood cells
RBC	Red blood cell
RBM	Roll Back Malaria
RR	Relative risk
SP	Sulfadoxine-pyrimethamine (Fansidar®)
STI	Sexually transmitted infection
TB	Tuberculosis
TBA	Traditional Birth Attendant
TNF-α	Tumor necrosis factor-α
UBOS	Uganda Bureau of Statistics
UN	United Nations
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
UVRI	Uganda Virus Research Institute
VCAM-1	Vascular adhesion molecule-1
WBC/s	White blood cell/s
Wbcc	White blood cell count
WBGroup	World Bank Group
WHO	World Health Organisation
wk/s	Week/s
yr/s	Year/s

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Chapter 1

1. INTRODUCTION

Cerebral malaria is a severe manifestation of malaria. Not only does it have a high case fatality rate but survivors can develop neurological sequelae of various kinds and severities. This study examined the neurological sequelae of cerebral malaria in children and adults in Uganda. I designed and carried out the study in conjunction with several people and groups. In this thesis, I document the background to the study, the methodology and findings in the next six chapters as stated below.

Chapter 2 consists of a description of the epidemiology in Uganda and its severe manifestations. The literature on cerebral malaria is reviewed. An account of how the parasites are postulated to cause brain dysfunction is given. The findings of studies that have examined the neurological sequelae of cerebral malaria are summarised. This background leads onto the study rationale and hypotheses.

In Chapter 3, I mention the study objectives, and describe the study design and study sites. A detailed account of the case definition and selection processes is given. The data collection tools are discussed including their development and usage. The treatment of cerebral malaria was standardised to ensure that cases received similar care at the study hospitals. Details are also given of the data management procedures and the statistical analyses conducted.

The descriptive results are presented in Chapter 4. The types of neurological sequelae detected in child and adult survivors are described. The natural history of deficits is elaborated. In doing so, the descriptive study objectives are addressed.

Results of analytic statistical procedures are summarised in Chapter 5. Factors that are associated with the three outcomes of the study namely, mortality, early-onset sequelae and late-onset sequelae, are highlighted. The findings from regression analyses are summarised to show the factors that are independently associated with the outcomes and differences between children and adults.

Chapter 6, consists of a discussion of the major findings, their interpretation and relevance. Sources of error and biases are described and the ways in which they were avoided or reduced are given. The influences that they may have had on the findings are highlighted.

In Chapter 7, conclusions are made, an account of the practical study benefits is given and some areas that need further study are listed.

Chapter 2

2. BACKGROUND AND STUDY RATIONALE

2.1 Malaria – A global disease and an African burden

Malaria is recognised as the commonest parasitic infection of humankind. Around 500 million clinical cases of malaria occur annually resulting in the death of up to 1 million children or about 2700 deaths per day (Snow, Craig *et al.* 1999). Sub-Saharan Africa which is estimated to have a population of 682 million people at mid 2004 (about 10% of the world population) bears about 90% of the global malaria burden (WHO and UNICEF 2003; UNFPA 2004). The Global Fund reports that the proportion of people at risk of malaria, currently estimated at 41%, is increasing because of deteriorating health systems, increasing drug resistance to the commonly used antimalarials, and resistance to insecticides, among others (TheGlobalFund 2004).

The situation in Africa, particularly south of the Sahara is precarious. About 10% of hospital admissions and 20 to 30% of visits to doctors are malaria related (MalariaFoundationInternational 1998). The most lethal of the four human species of plasmodia, *P. falciparum*, causes most of the malaria in this region. The tropical climate is not only conducive for the rapid reproduction of the plasmodia-carrying mosquitoes, the *Anophelines*, but is also conducive for the development of the malaria parasite. These factors and others have an adverse effect on not only the lives of people through premature death but on the quality of life through morbidity and reduced productivity.

2.2 Epidemiology of Malaria in Uganda – A process in transition

Malaria is one of the major health problems in Uganda. With a Gross Domestic Product (GDP) in 2003 of US$ 6.2 billion, Uganda is one of the poorest countries (WBGroup 2004). Uganda's 24 million citizens, 90% of whom live in highly malaria-endemic areas, not only have to cope with poverty but have to contend with other major killer diseases such as HIV/AIDS, tuberculosis and diarrhoeal illnesses (UBOS 2003). The under-five mortality rate (period for this derivation was not obtained) is estimated at 159/1000 live births of which malaria is estimated to be

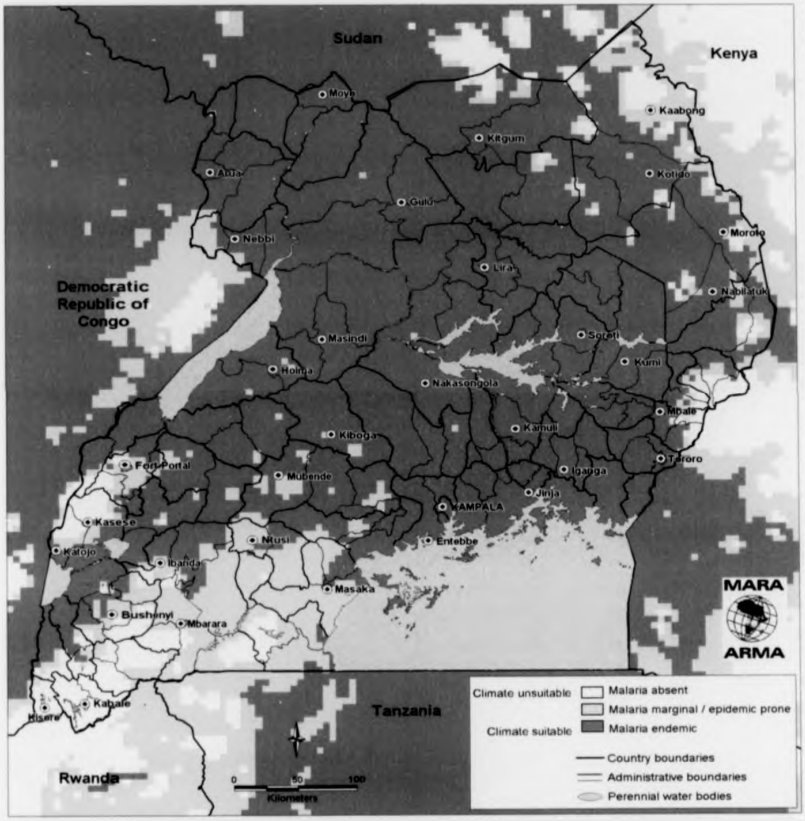
responsible for 37/1000 in high transmission areas and 18/1000 in low transmission areas. This translates to between 70,000 to 110,000 child deaths per year (Ministry of Health and WHO 1999). Malaria alone accounts for 20% of hospital admissions and 25-40% of all outpatient visits at health facilities in the country (RBM 2000).

Uganda lies astride the equator between 4 degrees north and 1.5 degrees south (area of 238,461 km^2), see Figure 1 for a map of Uganda. Temperatures fluctuate between 15 °C and 32 °C. Most parts of Uganda experience two rainy seasons; March to May and September to November contributing to a mean annual rainfall of 760 mm in the north east and 1,520 mm in the south, close to Lake Victoria. Most of Uganda is a plateau 900 m above sea level that lies between mountain ranges to the east and west, which are more than 3,000 m above sea level. About a fifth of the country is covered by water in the form of swamps, Lakes Victoria (the biggest fresh water lake in the world), George and Albert, and the River Nile. These climatic conditions are conducive for breeding of malaria vectors in almost all areas of the country below an altitude of 1,500 m. In addition, the ambient temperatures allow the speedy development of the parasite within the mosquito and humans. These factors enable high and stable malaria transmission in most parts of the country. Davidson (1955) measured spleen rates and crude parasite rates of all mosquito species in a population around Lira town, in the northern part of Uganda. His team found that over the four months, September to December 1962, the spleen rate ranged from 18% in infants 2 weeks to 2 months old, to 89% in the children between 12 months and four years of age. The crude parasite rates ranged from 21% in infants 2 weeks to 2 months old, to 98% in those aged 2 to 4 years. Figure 2 shows a climate-based distribution model of malaria transmission in Uganda compiled by a project called "Mapping Malaria Risk in Africa / Atlas du Risque de la malaria en Afrique".

Map 2.1: Map of Uganda showing the four districts in which the study hospitals are located

Source: This map is a product of the MARA/ARMA collaboration and was downloaded in October 2004

Uganda: Distribution of Endemic Malaria



This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za) July 2001 Medical Research Council PO Box 17120 Congella 4013 Durban South Africa CORE FUNDERS of MARA/ARMA International Development Research Centre Canada (IDRC) The Wellcome Trust UK South African Medical Research Council (MRC) Swiss Tropical Institute Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR) Roll Back Malaria (RBM) Malaria distribution model Craig M H et al 1999 Parasitology Today 15 105-111 Topographical data African Data Sampler WRI http://www.igc.org/wri/sdis/maps/ads/ads_ida.htm

Map 2.2 Distribution of Malaria transmission in Uganda

Source: This map is a product of the MARA/ARMA collaboration and was downloaded in October 2004

Generally speaking, in the colder and higher south-western highlands of the country malaria transmission is unstable; Hall and Langlands (1975) reported a crude parasite prevalence in Kigezi, 1966-67 of 8.1%. Areas with unstable transmission such as the south-east highlands have experienced epidemics such as those in 1994 (Mouchet, Manguin *et al.* 1998) and 1998 (Kilian, Langi *et al.* 1999; Lindblade, Walker *et al.* 1999). The epidemic in Kabale district (altitude of 1500-2400 m; 850-1200 mm of rainfall annually; average daily minimum and maximum temperatures of 9.8-12.6°C and 23.2-24.4°C respectively) began in February 1998 and peaked in March. The reported malaria incidence recorded at 5 rural health clinics at the peak of the epidemic was about 3 times greater than the average incidence for the previous 5 years (about 43 clinical cases of malaria per 1000 compared with 17 cases per 1000 between 1992-1997). The mean entomological inoculation rate during the epidemic, December 1997 to July 1998, was 0.41 infectious bites per person which the authors say was responsible for the increased incidence of malaria. (Lindblade, Walker *et al.* 1999)

All four species of Plasmodium that affect people occur in Uganda. *P. falciparum* is the predominant species with a frequency among positive blood-slides of 98.6% in Apac, 96.5% in Kampala, 99.3% in Rukungiri and 97.6% in Kabarole (Langi and Oryema 1994). *P. malariae* is less frequent than *P. falciparum* but more common than *P. ovale* and *P. vivax*. The major malaria vectors are *Anopheles gambiae s.l.* (the most efficient plasmodium carrier) and *A. funestus*. Between May and June 1992 and 1993, the relative indoor resting frequency of *An. gambiae s.l.* was 99% in Rukungiri, 98.9% in Kampala, 65.6% in Apac and 94.4% in Kabarole (in their report the authors did not specify the mosquito-catching method used). Other mosquito species that do occur include *A. pretoriensis, A rhodesiensis, A. christyi, A. pharoensis* and *A. rivulorum*.

Apart from the optimal climatic conditions for vector and parasite, and the highly anthropophic malaria vectors, there are other factors that have contributed to the widespread and increasing occurrence of malaria. The guerrilla war of the late 70s and mid 80s destroyed some of the health infrastructure that had been in place to cope with the burden of diseases in the country; malaria control efforts were

minimal with little motivation and few financial resources for vector control. In the post-war period, 1986 onwards (though there still remain some areas of insecurity in the northern parts of the country) much development has occurred. Roads have been constructed, dams built, multi-storied buildings erected, more areas cultivated, swamps drained and forests cleared, to mention a few changes. Mouchet *et al.* (1998) reviewed hospital records at Kisizi Mission Hospital located in the south-western highland area of Uganda and found that there has been a constant increase in the annual number of outpatients and inpatients seen at the hospital with malaria since 1968. Nineteen cases were treated as inpatients in 1968 and 8,580 as outpatients. Similar figures for 1976 (8 years later) were 215 inpatients (up 11-fold) and 16,219 outpatients (up 2 fold); in 1992 (16 years later) there were more than 2,900 inpatients (up 13-fold) and 22,344 outpatients (up 1.4 times); and in 1994 (2 years later) there were 4,875 inpatients (up 1.7 times) and 27,491 outpatients (up 1.2 times). Some reasons for this increasing frequency the authors say include rainfall excesses, migratory flow (inhabitants moving down into the valleys in search of arable land) and the cultivation of papyrus marshes in the valleys with food crops providing more conducive breeding sites for *A. gambiae*.

Another factor which has contributed to a greater burden of malaria is the migration of people from rural areas with low transmission intensities like the highland areas into towns like Kampala, Jinja, Masaka and Mbarara in search of jobs and better opportunities. These "economic migrants" are likely to have little immunity to malaria and during the course of their stay in these towns* that are located in areas where malaria transmission occurs go on to experience more episodes of malaria, of both the simple and severe forms. The population of the country increased from 4.7 million in 1950 to 15.5 million in 1985, at an average rate of about 3.5% per year (UN 1985). The increase in population size and subsequent changes in the population structure, placing a greater number of children at risk, will also have contributed to the increase in malaria frequency. The appearance of plasmodia resistant to chloroquine, the commonest and cheapest antimalarial in the country, has played a role in the increasing burden of malaria. It is not clear when chloroquine resistance was first noticed in the country. The East African Network for Monitoring Antimalarial Treatment (EANMAT) has studied the efficacy of

* Many towns in Uganda are not very urbanised and are a diffuse collection of buildings

chloroquine at sentinel sites in Uganda. Their results showed that using chloroquine in patients aged 6 to 59 months between 1998 to 2000, the proportion of late treatment failures (i.e. the presence of parasitaemia and fever after 4 days) was up to 31% (EANMAT 2003). All these factors mentioned are contributing to the epidemiology of malaria in Uganda and changing it.

2.3 Manifestations of Severe malaria and Acquired immunity to malaria

Malaria can be classified as simple or severe (another classification is uncomplicated and complicated malaria). A person with a fever attributable to plasmodial infection is said to have simple malaria. Severe malaria on the other hand, is a collection of clinical syndromes that have a high mortality (> 5%) despite adequate medical intervention (Newton and Krishna 1998). A list of criteria that define a case of severe malaria has been compiled under the auspices of the World Health Organisation (Warrell, Molyneux *et al.* 1990; WHO 2000). A subject with any one of the defining manifestations listed in Table 2.1 is said to have severe malaria as long as the manifestation(s) are attributable to *P. falciparum* infection by the identification of asexual forms of the parasite in blood and after the exclusion of other conditions that can cause the manifestation(s). The other supporting manifestations listed in the same table are features that often accompany the defining criteria either singly or in combination.

Table 2.1: Manifestations of severe malaria as defined by Warrell et al. (1990).

Defining criteria of severe disease
1. Cerebral malaria (unrousable coma)
2. Severe normocytic anaemia
3. Renal failure
4. Pulmonary oedema
5. Hypoglycaemia
6. Circulatory collapse, shock
7. Spontaneous bleeding/disseminated intravascular coagulation
8. Repeated generalised convulsions
9. Acidaemia/acidosis
10. Malarial haemoglobinuria
Other supporting manifestations
1. Impaired consciousness but rousable
2. Prostration, extreme weakness
3. Hyperparasitaemia
4. Jaundice
5. Hyperpyrexia

Several host and parasite factors appear to operate via separate or similar mechanisms to result in a host's gradual acquisition of clinical immunity to malaria and its severe manifestations. A hypothesis said to have first been proposed by Robert Koch in 1900 attributed acquired immunity to the gradual and cumulative build-up of an adequate repertoire of specialised immune cells (i.e. memory and effector cells) in response to a repertoire of parasitic antigens to which the host was previously exposed (Koch 1900c; a; b). Implying that the parasite does not elicit an adequate response from the host's immune system until such a time that the host can call upon a variety of immune responses, or possibly, one large but effective response, for which the parasite has no answer. The development of this form of immunity would depend on many exposures to the parasite, to different strains of the parasite, to different developmental stages of the parasite in the host and of course, a functional host immune system. It is postulated that such exposures would have to be sustained over long periods of time (Baird, Jones *et al.* 1991). As enough clinical immunity is acquired the risk of severe malaria should decrease. In addition, with more frequent contacts with the parasites, as in areas with high malaria endemicity, a host should acquire clinical immunity to severe malaria at a faster rate than a host in an area of low endemicity. This is exemplified by observations that in hyper-holoendemic malaria areas the frequency of severe malarial manifestations rises to a peak between 2-6 years then declines steadily until about 10 to 15 years of age after which the occurrence of episodes of severe malaria is infrequent (Rogier and Trape 1993).

Alternatively, clinical immunity to malaria could be more dependent on the maturity of the host's immune system and less so on the number of exposures to plasmodia. This alternative hypothesis of age-dependent acquired immunity stems from observations made by some authors that adults who previously resided in non-malarious regions developed effective clinical immunity to malaria after only a few number of exposures to malaria parasites (Baird, Jones *et al.* 1991; Baird 1998). They developed clinical immunity at a faster rate than children exposed to the same levels of malaria transmission. It is possible that both mechanisms, i.e. exposure-dependent and age-dependent, are equally important and somehow the acquisition of immunity appears to influence the spectrum of severe disease seen in a given population.

2.4 Epidemiology of Cerebral malaria

Cerebral malaria (CM) represents a clinical syndrome which Warrell *et al.* in 1990 redefined as *"Unrousable coma not attributable to any other cause in a patient with falciparum malaria"*. Warrell and Gilles (2002) more recently make a distinction between two definitions; a "research" definition and a "practical" one. The latter defines cerebral malaria as "any impairment of consciousness or convulsions in a patient exposed to malaria". The research definition is more rigorous and states a number of requirements: i) Unrousable coma (Glasgow Coma Score < 10/14) that persists for more than 6 hours after a generalised convulsion, ii) Asexual forms of *P. falciparum* in the blood smear, iii) Exclusion of other causes of coma by history, cerebrospinal fluid examination, cultures and serology and iv) in fatal cases, confirmation of typical brain histopathology, sequestered infected erythrocytes, by post-mortem needle necropsy.

Cerebral malaria occurs in all areas with conditions suitable for the propagation of *Plasmodium falciparum*. There have been reports of patients in which the loss of consciousness has been attributable to *P. vivax* in India and China (Fitz-Hugh, Pepper *et al.* 1944; Gandhi, Nayak *et al.* 1990; Sachdev 1996; Beg, Khan *et al.* 2002). CM is a deadly disease with a case fatality rate that can reach up to 50% (Warrell 1997). Studies have been able to determine the proportion of cerebral malaria among, paediatric admissions i.e. inpatients only, or all cases of falciparum malaria seen at a hospital i.e. both outpatients and inpatients. Table 2.2 summaries and illustrates the geographical occurrence of cerebral malaria. In children, the proportion of cerebral malaria among those admitted to paediatric units ranges from about 2.3% reported in Malawi to 25.4% in Côte d'Ivoire among children less than 5 years (Nkhoma, Nwanyanwu *et al.* 1999; Pagnoni and Delacollette Lebrun 2002). If a more selective denominator is used, for example children admitted with falciparum malaria, the proportion with cerebral malaria documented is higher, 51%, as observed in The Gambia (Brewster et al., 1990). Murphy and Breman reviewed 35 studies of cerebral malaria in sub-Saharan Africa and estimate the annual incidence of CM to be 6.1 cases per 1,000 children aged below 5 years and 2.7 cases per 1,000 children aged 5 to 9 years (Murphy and Breman 2001).

Table 2.2: Summary of studies that have documented the frequency and case fatality ratio of cerebral malaria

Reference	Country	Number of cases	Cerebral malaria definition*	Denominator (population at risk)	Frequency of CM (%)	Case Fatality (% of cases)
Children						
Mengistu *et al.* (1979)	Ethiopia	52	Practical	435 cases of malaria seen at the study hospital	12	26.9
Steele *et al.* (1995)	Ghana	285	Practical	2688 children aged less than 14 years hospitalised at the study hospital	10.6	6
Commey *et al.* (1980)	Ghana	43	Practical	All cases admitted to the paediatric unit of the study hospital	7	4.6
Thapa *et al. (1988)*	India	40	Practical	Not ascertained	-	32.5
Ahmad *et al. (1986)*	India	30	Practical	Not ascertained	-	20
Berkley *et al.* (1999)	Kenya	297	Practical	555 children admitted with non-traumatic impairment of consciousness	53.5	23.4
Nkhoma *et al.* (1999)	Malawi	199	Practical	8600 children aged less than 5 years hospitalised to the study hospitals	2.3	11.3 to 15.3
Molyneux *et al. (1989)*	Malawi	131	Research	Not ascertained	-	15
Olumese *et al.* (1999)	Nigeria	103	Research	Not ascertained	-	22.3
Bondi (Bondi 1992)	Nigeria	78	Research	Not ascertained	-	20.5
Ikpatt *et al.* (1990)	Nigeria	75	Research	8,341 children admitted to the children's emergency room	0.9	20

Table continued overleaf

* The case definition used was either the strict "research" one or a broader and "practical" one.

Table 2.2 continued

Author, year	Country	Number of cases	Cerebral malaria definition	Denominator (population at risk)	Frequency (%)	Case Fatality (%)
Stace *et al.* (1982)	Papua New Guinea	68	Practical	Not ascertained	-	5.9
Schmutzhard & Gerstenbran (1984)	Tanzania	66	Practical	7915 cases (all ages) of P. falciparum malaria seen at the study hospital	0.8	18.2
van Hensbroek *et al.* (1997)	The Gambia	624	Research	Not ascertained	-	21.5
Brewster *et al.* (1990)	The Gambia	308	Research	604 children admitted with falciparum malaria	51	14
Idro *et al.* (2004)	Uganda	100	Research	Not ascertained	-	7
Musoke (1966)	Uganda	20	Practical	Not ascertained	-	30
Pagnoni *et al.* (2002)[†]	Benin	42	Research	207 children admitted with severe malaria	14	9
	Burkina Faso	13	Research	201 children admitted with severe malaria	4.7	20
	Burundi	14	Research	104 children admitted with severe malaria	9.7	21
	Cameron	3	Research	69 children admitted with severe malaria	4	-
	Côte d'Ivoire	43	Research	139 children admitted with severe malaria	25.4	11.6
	Ethiopia	16	Research	101 children admitted with severe malaria	9.7	25
	Nigeria	48	Research	163 children admitted with severe malaria	22.7	10.4
	Togo	11	Research	101 children admitted with severe malaria	6.6	-
	Uganda	13	Research	75 children admitted with severe malaria	10	-
	Zambia	15	Research	70 children admitted with severe malaria	11.5	-
Adults						
Elamin (1981)	Zambia	34	Practical	450 cases of falciparum malaria	7.5	-
Olweny *et al.* (1986)	Zambia	56	Practical	Not ascertained	-	9
Lutalo & Mabuwa (1990)	Zimbabwe	NS	Practical	162 patients aged 10 years and above treated for malaria at the study hospital	39.2	17
Niyongabo *et al.* (1994)	Burundi	31	Practical	Not ascertained	-	22.6
Karbwang *et al.* (1995)	Thailand	64	Practical	102 cases of severe falciparum malaria	62.7	-

[†] A multi-centre study conducted in ten countries and recruited a total of 1,230 children aged 6 to 59 months

In adults, the proportion of inpatients seen with falciparum malaria that have cerebral malaria ranges from 7.5% in Zambia to 39.2 in Zimbabwe (Elamin 1981; Lutalo and Mabuwa 1990). Karbwang et al. (1995) documented a proportion of 62.7% among cases admitted with severe malaria over a two year period in Thailand. In the same Table, the case-fatality ratios (CFRs) of cerebral malaria are given and show much variation. A pooled CFR from the review by Murphy and Breman (2001) was calculated to be 19.2% (95% CI 16.2-22.3, n=3,275). There appears to be some relation between fatality and age, in which older children and adults have a higher mortality (Kiszewski and Teklehaimanot 2004).

The occurrence of cerebral malaria, as well as the proportion of severe malaria attributable to cerebral malaria in a population, appears to be influenced by the prevailing level of malaria transmission. Cerebral malaria generally tends to occur proportionally more often than the other manifestations of severe malaria in areas of low transmission intensity and less so in areas with high intensity (Marsh and Snow 1999). (Snow, Omumbo *et al.* 1997) In addition to this, within a population, cerebral malaria tends to occur at a relatively older age than severe anaemia. For example in an area in Senegal with low transmission the mean age of children with severe anaemia was 58 months and that for cerebral malaria was 102 months (Trape, Lefebvre-Zante *et al.* 1993) and in an area with high transmission in Kenya, the ages were 16.7 and 20.3 months respectively. (Snow, Omumbo *et al.* 1997)

2.5 Pathogenesis of Cerebral malaria

There have been a number of theories about the pathogenesis of human cerebral malaria. In the 1940s the "permeability" hypothesis was proposed suggesting that the features of cerebral malaria were due to an increase in the cerebral capillary permeability with outward leakage of plasma causing cerebral oedema and haemo-concentration in the capillaries. The result would be a local reduction the micro-circulating blood flow (Warrell, Molyneux *et al.* 1990). This hypothesis has been superseded by others as more knowledge about the mechanisms of this encephalopathy has been acquired. The current hypothesis is that of "sequestration" in which parasitised red blood cells (PRBCs) containing mature falciparum trophozoites are selectively sequestered in the micro-vasculature of the brain (MacPherson, Warrell *et al.* 1985; White and Ho 1992; Berendt, Tumer *et al.* 1994;

Esslinger, Picot *et al.* 1994). The mechanism that seems to be responsible for this process is cytoadherence, a property by which PRBCs express molecules on their surface that are responsible for their increased adhesiveness to host ligands on the capillary and post capillary walls. These erythrocyte surface membrane molecules are a high molecular mass family of proteins encoded by the *var* genes of *P. falciparum*. An example of such a protein is *P. falciparum* erythrocyte membrane protein-1 (Pfemp-1). It is localised primarily to parasite-induced "knobs" on the surface of PRBCs (Miller 1972; Aikawa, Rabbege *et al.* 1983; Warrell 1997; Newton, Hien *et al.* 2000). Host ligands for cytoadherence include leukocyte differentiation antigen CD 36, intracellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and endothelial leukocyte adhesion molecule-1 (E-selectin) (Turner, Morrison *et al.* 1994; Cegielski and Warrell 1997b). These host ligands are inducible or up-regulated when endothelial cells are exposed to appropriate cytokine stimuli. And in fact, plasma concentrations of cytokines such as tumor necrosis factor α (TNF-α) are elevated in adults and children with severe malaria and in some cases associated with coma. The role played by toxins such as TNF-α, in the overall dysfunction of the brain constitutes the "toxin" hypothesis (Grau, Piguet *et al.* 1989; Grau, Taylor *et al.* 1989; Kwiatkowski, Hill *et al.* 1990). The *var* genes seem to also be responsible for the adherence of non-parasitised red blood cells (NPRBCs) to parasitised ones, a property known as "rosetting" (Carlson, Helmby *et al.* 1990; Ringwald, Peyron *et al.* 1993; Newton and Krishna 1998). Other processes that are being evaluated include the accumulation of platelets in the microvessels of the brain (Grau, Mackenzie *et al.* 2003) and the role of the host's protective immune responses on endothelial cells and the blood brain barrier (Medana, Chaudhri *et al.* 2001; de Souza and Riley 2002; Artavanis-Tsakonas, Tongren *et al.* 2003).

The above processes contribute to the loss of consciousness in cerebral malaria sufferers via a number of postulated mechanisms (Clark, Rockett *et al.* 1991; Clark and Rockett 1994). The sequestered parasites in the cerebral venules alter the function of the neurones via metabolic derangements in the adjacent brain cells by competing for substrates such as glucose for their own metabolic processes and producing lactic acid (Newton and Krishna, 1998). The parasites may also produce toxins that may interfere with neuronal metabolism (Taylor, Day *et al.* 1998).

Seizures arising from the effect the parasites have on the cerebral cells can in turn contribute to coma. To a lesser degree, the systemic effects of *P. falciparum* infection including high-grade fever and hyponatraemia, also play a contributory role to the impairment of consciousness. These postulated mechanisms also contribute to the complications of cerebral malaria as highlighted in the next subsection.

2.6 Neurological sequelae of Cerebral malaria

Survivors of cerebral malaria may recover without any complications or may develop neurological sequelae of various kinds and severity. There is no standard definition for the neurological sequelae of cerebral malaria. However, in general any impairment of neurological or cognitive function attributable to preceding illness with cerebral malaria are the "neurological sequelae of cerebral malaria". Some authors have considered the neurological sequelae associated with falciparum malaria or severe malaria which encompasses impairments that result from the effects of severe malaria and not just cerebral malaria.

Neurological sequelae of CM can be gross, for example motor-sensory deficits such as hemiparesis; or they can be subtle, for example cognitive dysfunction such as attention disorders. The types of neurological sequelae which have been described are listed in Table 2.3. As shown, some deficits (a word I shall use interchangeably with sequelae) are present at discharge and others develop thereafter. Some sequelae are reversible and others appear to persist. There does not appear to be a clear distinction between the types in adults and those in children, though developmental sequelae occur in children by virtue of their under-developed brains. This list is by no means exhaustive and only serves to highlight the variety of the sequelae and a few of their characteristics.

The documented frequency of sequelae in children at discharge ranges from about 5 to 23% (Molyneux, Taylor *et al.* 1989; Carme, Bouquety *et al.* 1993; Steele and Baffoe Bonnie 1995; van Hensbroek, Palmer *et al.* 1997; Idro, Karamagi *et al.* 2004). A fewer number of studies have noted the proportion of adult survivors with sequelae. The proportion in this group ranges from about 5 to 10% (Warrell, Molyneux *et al.* 1990). A summary of studies that have examined the frequency of

neurological sequelae in cerebral malaria is given in Table 2.4 (the data here does not include those that have looked at sequelae in severe malaria).

Table 2.3: Summary of the types and selected characteristics of neurological sequelae in children and adults

Neurological Sequelae	Characteristics described in the literature		
	Age group*	Recovery documented	Detection†
A. Motor-sensory			
Spastic hemiparaesis	Children	Yes	At discharge
Residual epilepsy	Children	No	At discharge
Generalised hypotonia	Children		At discharge
Generalised spasticity of limbs	Children		At discharge
Cerebellar ataxia	Both	Yes	At discharge
Bilateral extrapyramidal tremor	Children		At discharge
Cerebral palsy	Children		At discharge
Cortical blindness	Children	Yes	At discharge
Aphasia	Children	Yes	At discharge
Monoparaesis	Children	Yes	At discharge
Hemichorea	Children	No	At discharge
Headache/dizziness	Children		At discharge
Facial nerve palsy	Children		At discharge
Myasthenia gravis-like syndrome	Children		At discharge
Dysarthria	Children	Yes	At discharge
Hearing loss	Children		At discharge
B. Cognitive			
Psychosyndrome	Children		At discharge
Memory impairment	Children		After discharge
Attention deficit disorders	Both	Yes	After discharge
Restlessness	Both		After discharge
Hallucinations	Children	Yes	After discharge
Aggressive behaviour	Children	Yes	After discharge
Depressive affect	Adults		After discharge
Personality change	Adults		After discharge
Subjective distress	Adults		After discharge
Impaired memory	Adults		After discharge
Emotional lability	Adults		After discharge
C. Developmental			
Mictutional disorders	Children		At discharge
Developmental regression	Children	No	After discharge
Mental retardation	Children	No	After discharge

* Documented in "children" aged 12 years and below or "adults" aged over 12 years or "both"
† Detected at time of discharge or sometime after discharge in a survivor who did not seem to have deficit(s) at discharge

Table 2.4: Table illustrating the proportions of survivors of cerebral malaria who developed neurological sequelae and the number whose sequelae improve or persist during the study period.

Study	No. of survivors (Type of sequelae*)	No. with sequelae at discharge (% of survivors)	No. who develop sequelae later (Period after discharge)	No. whose sequelae improve (Period between detection and disappearance)	No. whose sequelae persist (Follow-up period)
Cross-sectional studies					
(Schmutzhard and Gerstenbrand 1984)	54 children aged 6mths-15yrs (MS)		10 (within 6 months)		
(Molyneux, Taylor *et al.* 1989)	111 children aged 7mths-10yrs (MS)	12 (11)		4 (4 wks)	7 (4 wks)
(Ikpatt, Asindi *et al.* 1990)	60 children aged 6mths-11.5yrs (MS)	10 (17)		10 (Not specified)	
(Olumese, Gbadegesin *et al.* 1999)	80 children aged 11mths-5yrs (MS)	12 (15)		12 (within 1 mth)	
(Idro, Karamagi *et al.* 2004)	93 children aged 3mths-11yrs (MS)	5 (5.4)			
(Abdulla, Sokrab *et al.* 1997)	A case series of 30 adults aged 16-57yrs with cerebellar ataxia	6 had ataxia	24 (within 3-20 days)		
Retrospective studies					
(Steele and Baffoe Bonnie 1995)	187 children aged <14 yrs (MS)	42 (23)			17 (12 wks)
Prospective studies					
(Brewster, Kwiatkowski *et al.* 1990)	265 children (MS)	35 (13)		12 (24 wks)	23 (24 wks)
(Bondi 1992)	62 children (MS & CS)	9 (14.5)	2 (within 12 mths)	5 (within 12 mths)	6 (within 12 mths)
(Carme, Bouquety *et al.* 1993)	145 children (MS)	13 (9)	18 (within 27 mths)	7 (within 27 mths)	
(van Hensbroek, Palmer *et al.* 1997)	490 children aged 1-9yrs (MS & CS)	114 (23)	12 (4 wks)	84 (4 wks)	42 (4 wks)
			4 (24 wks)		20 (24 wks)
					17 (72 wks)
(Karbwang, Tin *et al.* 1995)	64 adults aged 15-65yrs (MS)	3 (4.6)		2 (within 1 mth)	

* MS, referring to Motor-sensory sequelae; and CS, referring to Cognitive sequelae.

Survivors can develop sequelae immediately upon recovery from coma in which case they are detectable at time of discharge or they can occur weeks after. The table illustrates the timing of sequelae in studies that were able to show this. About 50% of survivors who are discharged with deficits have been shown to improve within 12 months (Mung'Ala-Odera, Snow *et al.* 2004). The commonest deficits identified in children detected at various periods have been: cortical blindness within three months after discharge and seizures within 27 months post-discharge (Carme, Bouquety *et al.* 1993); seizures within 12 months after discharge (Bondi 1992); ataxia at one month after discharge, weakness of muscles (i.e. paresis) at six and eighteen months after discharge (van Hensbroek, Palmer *et al.* 1997); and paralysis of either the right or left side of the body (i.e. hemiplegia) at discharge (Brewster, Kwiatkowski *et al.* 1990). Detection of motor-sensory neurological deficits has involved neurological clinical examination by study or routine physicians. Special batteries of tests have been employed to detect cognitive and developmental forms of neurological dysfunction (Holding, Stevenson *et al.* 1999; Holding, Taylor *et al.* 2004). To be useful, these have to be standardised to reflect the socio-economic and educational background of the population in which they are employed.

2.6.1 Patho-physiology of the neurological sequelae of cerebral malaria

The causes of neurological sequelae of cerebral malaria are largely unknown. It is probable that a number of factors contribute to the aetiology of sequelae. Sequelae arise because of damage or destruction of neural tissue which can either be by necrosis or apoptosis (Newton and Krishna 1998). The role of ischaemia in the production of brain damage is well-known. Reduced cerebral perfusion pressure which causes reduced delivery of blood to the enclosed brain has been associated with severe neurological damage in Kenyan children (Newton, Crawley *et al.* 1997). The perfusion pressure to the brain is maintained by a complex autoregulatory mechanism which could malfunction in cerebral malaria patients. The posterior parieto-temporal region of the brain is particularly prone to ischaemia when oxygen supply to the brain is compromised by either impaired autoregulation, severe anaemia, inadequate cerebral blood flow, or raised intracranial pressure. This part of the brain lies between the posterior and middle cerebral arteries and takes part in the perception of light. Children have been observed to develop cortical blindness which

would result from dysfunction of this aspect of the cerebral cortex. At a minute level, hypoxia can be generated by impaired delivery of oxygen to brain cells because of the congested microvessels clogged with parasitised red blood cells adhering to vesicular endothelia (cytoadherence) and non-parasitised cells (rosetting) or an interruption of the normal mechanism of oxygen transfer from the oxyhaemoglobin of the PRBC to the tissues (Maegraith 1951).

Recurrent convulsions that occur in both children and adults (although the frequency in children is higher than adults) during severe malarial infection can cause cerebral ischaemia and in turn also contribute to the coma of cerebral malaria. Crawley *et al.* (1996) found that of the 10 children with minimal clinical features of convulsions, 5 of them regained consciousness within 6 hours of treatment with intravenous diazepam suggesting that their coma was partly due to subclinical seizure activity. A prolonged seizure causes increased cerebral metabolism with the depletion of adenosine triphosphate (ATP), glucose, oxygen and the accumulation of lactic acid. This stimulates an increase in cerebral blood flow with a subsequent increase in cerebral blood volume adding to the intracranial hypertension that can potentially complicate cerebral malaria. The hippocampus is particularly prone to seizure-induced damage and this area of the brain is important for short and long-term memory. Furthermore the convulsions in children appear to be related to the cerebral dysfunction caused by falciparum malaria and not febrile convulsions since the majority occur at rectal temperatures less than 38°C (54%) and few of them are associated with either hypoglycaemia or any metabolic derangement. Crawley *et al.*, (1996) in their study of 65 Kenyan children noted that 10 children (25%) had seizures with subtle or subclinical convulsive activity, which is a recognised feature of prolonged generalised status epilepticus. Thus the overall frequency of convulsions in children (and possibly in adults) based on observed tonic convulsive activity may be an underestimate of the true frequency of seizures especially since the ictal features can easily be missed unless sought and many of the hospitals in Africa do not have electroencephalogram (EEG) facilities.

Anaemia if severe, (in infants especially) would cause a generalised impairment in oxygen supply. If such unconscious patients are not adequately attended to while in hospital, for example ensuring a patent airway or providing appropriate blood

oxygenation, then the ischaemic damage to the cerebral cells could be worsened or precipitated by underlying severe anaemia.

Toxins have been postulated to also contribute to the aetiology of neurological sequelae. To-date the toxins documented have been chemicals produced by the host cells. Using a mouse model, Clark et al. (1983) showed that reactive oxygen species are produced during malaria infection and proposed that if this occurs in humans as well, reactive oxygen species could cause coma and damage to local tissues like the brain. In adults, monocyte generation of reactive oxygen species has been found to be elevated adding some credence to Clark's hypothesis (Dubey, Rai *et al.* 1991). Reactive oxygen species can also induce apoptosis, a process by which human cells respond to a programmed trigger to destroy themselves. Nitric oxide (NO) has been examined as a possible cause of impaired neuronal function. It is hypothesized that it is induced (TNF-α) in endothelial cells of the vessel walls at sites of parasite sequestration, diffuses through the blood brain barrier and reaches the neurones. This would subject the neurones to a surplus quantity of nitric oxide in addition to their own glutamate-induced network of nitric oxide. These additional and uncontrolled quantities of NO could cause impaired neurotransmission and coma as well as neurological damage and sequelae (Lipton, Choi *et al.* 1993). Other toxic substances that could be implicated in the causation of neuronal damage are excitotoxins. When produced in normal amounts, these endogenous neurotransmitters participate in the excitation of neurones and the transmission of neuronal stimuli. However when in larger than normal quantities they are toxic to neuronal cells. Hypoxia, hypoglycaemia and convulsions, which have been associated with neurological sequelae, can cause the release of these neurotransmitters.

Hypoglycaemia is recognised as one of the severe manifestations of falciparum malaria and it is a known cause of coma. It can also contribute to neuronal damage. Intra-erythrocytic trophozoites actively compete for glucose with erythrocytes and adjacent host cells potentially impairing delivery of glucose to brain cells. This competition for substrates may not affect homeostasis systemically but may have profound effects on local metabolism where PRBCs are localised to capillaries. Depriving the neighbouring cerebral cells of glucose in this manner would impair

their function and could even cause them to self-destruct (apoptosis). The added effect of hyperinsulinaemia induced by quinine administration during therapy for severe malaria could amplify this situation if hypoglycaemia is not detected and corrected quickly enough.

2.6.2 Risk factors for neurological sequelae

Investigators have elucidated, with different degrees of success, some of the factors that determine sequelae (Bondi 1992; van Hensbroek, Palmer *et al.* 1997; Holding, Stevenson *et al.* 1999; Idro, Karamagi *et al.* 2004). In Table 2.5 is a list of some risk factors that have been identified thus far. Holding *et al.* (1999) examined neurological deficits of the cognitive type that occurred during follow up with 87 matched pairs of cases and controls. Cases were children who had impaired consciousness (BCS $\leq$ 4) due to severe malaria. Van Hensbroek *et al.* (1997) in their study in The Gambia obtained sufficient information from 145 survivors of cerebral malaria (90 children were followed up) to determine factors that were associated with neurological deficits. Factors which were consistently identified as risk factors are hypoglycaemia on admission, multiple seizures while in hospital (described as multiple witnessed seizures), and longer duration of coma.

2.7 Study rationale

Given this background information, there are possible reasons for there to be a difference in the frequency of sequelae in children and adults. These include:

Case fatality ratio of cerebral malaria: The CFR appears to differ between children and adults. In African children, the overall mortality of strictly defined cerebral malaria is 18.6% (95% CI 16.3-21.0) (Newton and Krishna 1998). In adults the mortality for "pure" cerebral malaria i.e. without evidence of vital organ dysfunction, is 8%. However when associated with acute renal failure (a manifestation which is rare in children) and metabolic acidosis, the mortality rises to 50% (Newton, Hien *et al.* 2000). If more adults are dying then there is a possibility that a higher proportion of adult patients die before they can develop sequelae.

Table 2.5: A list of the risk factors for neurological sequelae of cerebral malaria specifying the comparisons groups and period during which sequelae where detected

Factor	Definition / description of determinant*	Relative risk estimate (95% CI) or probability of association (proportion)	Type of sequelae used as outcome	Period when sequelae were detected	Reference
Demography and history					
Age at admission	≤24 mths	OR 0.71 (0.20-2.57)	CS	3.5 to 5.8 yrs after illness	(Holding, Stevenson *et al.* 1999)
Previous admission	For severe malaria	Adjusted OR 5.6 (1-31.6)	MS	At discharge	(Idro, Karamagi *et al.* 2004)
Examination on admission					
Body temperature	Mean rectal temperature on admission (39.3 °C compared with 38.8 °C)	Statistically significant association	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
Depth of coma	BCS score 0 or 1	Adjusted OR 7.4 (1.8-29.7)	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
Laboratory information on admission					
Hypoglycaemia	Blood glucose ≤2.6 mmol/L	OR 5.40 (1.46-19.91)	CS	3.5 to 5.8 yrs after illness	(Holding, Stevenson *et al.* 1999)
	Plasma glucose ≤2.2 mmol/L	Statistically significant association (7/51)	MS & CS	At discharge up to 12 months later	(Bondi 1992)
	Blood glucose <2.2mmol/L	Statistically significant association (8/20)	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
	Repeated hypoglycaemia	Statistically significant association (4/20)	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
Parasitaemia	Hyperparasitaemia of >500,000 parasites per 100 RBC	OR 0.48 (0.06-4.05)	CS	3.5 to 5.8 yrs after illness	(Holding, Stevenson *et al.* 1999)
Haemoglobin concentration	≤5 g/dL	OR 1.27 (0.37-4.39)	CS	3.5 to 5.8 yrs after illness	(Holding, Stevenson *et al.* 1999)
White blood cells	Median white blood cell count (18.2 x 10^9/L compared with 11.3 x 10^9/L)	Statistically significant association	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)

* Value in group with sequelae compared with value in group without sequelae

Table 2.5 continued

Factor	Definition / description of determinant	Relative risk estimate (95% CI) or level of association (proportion)	Type of sequelae used as outcome	Period when sequelae were detected	Reference
While in hospital					
Witnessed seizures	A total number of ≥3 seizures	OR 5.18 (0.63-42.43	CS	3.5 to 5.8 yrs after illness	(Holding, Stevenson *et al.* 1999)
	Severe seizures	Statistically significant association (9/51)	MS & CS	At discharge up to 12 months later	(Bondi 1992)
	Multiple convulsions	Statistically significant association (13/20)	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
	Multiple convulsions	Adjusted OR 7.1 (2.2-22.7)	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
	Multiple convulsions	Adjusted OR 9.2 (1.7-50)	MS	At discharge	(Idro, Karamagi *et al.* 2004)
	Focal convulsions	Adjusted OR 7.3 (1.1-50)	MS	At discharge	(Idro, Karamagi *et al.* 2004)
Duration of coma	≥24 hrs to regain ability to localise painful stimuli	OR 3.41 (0.97-11.96)	CS	3.5 to 5.8 yrs after illness	(Holding, Stevenson *et al.* 1999)
	Mean duration of unconsciousness (129.3 hrs compared with 55 hrs)	Statistically significant association	MS & CS	At discharge up to 12 months later	(Bondi 1992)
	Median coma duration before admission (12 hrs compared with 6 hrs)	Statistically significant association	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
	Median duration of coma (116 hrs compared with 24 hrs)	Statistically significant association	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
	Comatose for ≥48 hrs	Adjusted OR 13.4 (3.4-52.4)	MS	At discharge up to 18 months later	(van Hensbroek, Palmer *et al.* 1997)
Respiratory distress	Had one or more episodes	OR 0.51 (0.15-1.79)	CS	3.5 to 5.8 yrs after illness	(Holding, Stevenson *et al.* 1999))
Duration of hospital stay	Mean duration of hospital stay (4.34 days compared with 2.1 days)	Statistically significant association	MS & CS	At discharge up to 12 months later	(Bondi 1992)
At discharge					
Neurological deficits at discharge		OR 19.6 (4.64-84.65)	CS	3.5 to 5.8 yrs after illness	(Holding, Stevenson *et al.* 1999)

Seizures: Children have a higher incidence of seizures and it is estimated that about 50 - 80% of them present with seizures whereas the range in adults is 20 – 50% (Newton and Krishna 1998; Newton and Warrell 1998). Adults are less likely to have status epilepticus and less likely to have evidence of subtle seizure activity. If there is an association between seizures and neurological sequelae then this would predispose more child survivors to neurological sequelae than adults.

Hypoglycaemia: Hypoglycaemia is found more frequently in children (20%) than adults (8%) with cerebral malaria (Newton and Krishna 1998). Hypoglycaemia causes coma and can precipitate convulsions. In this way hypoglycaemia can be associated with sequelae (Brewster, Kwiatkowski *et al.* 1990; Bondi 1992) and contribute to a higher frequency of sequelae in children.

Brain development: The adult brain is more mature but less malleable than at a younger age. Therefore if neuronal injury and recovery is related to either or both of these qualities, it is feasible that the frequency of neurological deficits can differ between children and adults.

Immunological basis of brain injury: The role of a more competent immune system in the pathogenesis of cerebral malaria has been postulated. If CM affects the brain more severely when the immune responses are more developed as would be the case in older subjects, then the risk of neurological deficits in survivors who be related to age of onset of disease.

This study sets out to examine differences in the occurrence and characteristics of neurological sequelae in children and adults in Uganda in an attempt to provide more knowledge on the determinants of neurological sequelae. In this way, the study can contribute to a better understanding of the pathways leading to deficits and consequently better strategies for prevention.

2.7.1 Study hypotheses

Null hypothesis: The characteristics (type, timing, reversibility) and risk factors of the neurological sequelae that follow an episode of cerebral malaria are similar in children and adults in Uganda.

Alternate hypothesis: The characteristics (type, timing, reversibility) and risk factors of neurological sequelae that follow an episode of cerebral malaria are dissimilar in children and adults in Uganda.

Chapter 3

3. METHODOLOGY

3.1 Study objectives

3.1.1 General objective

To determine the natural history of neurological sequelae in Uganda children and adults comparing both groups for differences and determine the risk factors for sequelae.

3.1.2 Specific objectives

1. To determine the kinds of sequelae that occur in Ugandan children and adults
2. To determine the duration between cerebral malaria and the occurrence of sequelae
3. To determine the proportion of survivors of cerebral malaria who have deficits that go on to improve
4. To determine the duration between cerebral malaria and the regression of sequelae in subjects who have sequelae.
5. To identify differences in the types and characteristics of neurological sequelae in children and adults.
6. To determine risk factors for neurological sequelae among children and adults, and identify any differences.

3.2 Sample size estimation

Sample size was estimated according to the formula of Rigby and Vail for a two-sample comparison of proportions (Rigby and Vail 1998).

$$N = \frac{\{p_1 \times (1-p_1)\} + \{p_2 \times (1-p_2)\}}{(p_1-p_2)^2} \times M$$

where,

N = the number of subjects per group (assuming that each group is equal in size)

p_1 = the proportion with the outcome of interest in group 1

$1-p_1$ = the proportion without the outcome of interest in group 1

p_2 = the proportion with the outcome of interest in group 2

$1-p_2$ = the proportion without the outcome of interest in group 2

M = a number derived by the authors for sample size calculations for common values of α and $(1-\beta)$. The precise formula for "M" is not given by the authors. The value of 7.8 substituted for M corresponded to a study power $(1-\beta)$ of 0.80 and significance level (α) of 0.05 (two-tailed).

The size of the study was that needed to detect a 3-fold difference in the proportion of neurological sequelae between children (5%) and adults (15%). Putting these values in the formula, it was estimated that a sample of 274 subjects of two equal groups would be sufficient. An additional 30% was added to account for deaths (20%) and losses to follow-up (10%) giving a total sample size of 364 patients with the case definition.

3.3 Study design

To enrol the required number of cases estimated from the sample size calculation (N=364), a multi-centre study design was adopted since none of the study sites visited during the preparation of the study had sufficient cases on their own. The combination of the five hospitals, Kabale, Mutolere, Mulago, Mbale and Masaka recorded 863 cases of cerebral malaria between January and December 1999 (1997 in the case of Mulago hospital). Mulago hospital alone recorded 625 cases of whom 145 were above 12 years of age. Mulago, which is the national referral hospital and the main medical teaching hospital, was the more obvious option for such a study because of the large number of cerebral malaria cases seen there in both children and adults. However, the Principal Investigator, who has worked there for several years, did not use this site for a number or reasons. These include:

i. Mulago hospital is huge with a capacity of 1,500 beds, and the logistics of conducting a study of this nature involving the 3 paediatric and 3 adult medical wards would require much input in terms of time, money and manpower. Some staff would need to be hired to assist in case management since the regular staff have too much to do already.

ii. Much research is conducted at the hospital by postgraduate medical students as well as other staff. Some of the junior staff are fatigued by the numerous

studies that they have to participate in and as a result, it was my personal opinion that this study which required intensive patient care would need an environment in which the staff were eager and motivated to participate.

iii. Follow-up and tracing of survivors would be difficult to organise since the population from which the cases are coming from is very diverse and covers a large catchment area.

iv. It would be difficult to determine the factors that contribute to any selection bias in such a heterogeneous population.

v. The additional research work could adversely affect the overall service delivery and output in the very busy paediatric and medical wards.

In comparison, the advantages of conducting the study at the selected district level hospitals are:

i. They are located in or close to epidemic-prone areas where much of the population is supposed to be relatively non-immune to malaria and this would increasing the probability of getting patients who have a wide age distribution.

ii. It was anticipated that the *El Nino phenomenon* (ENSO) was likely to occur during the study period (between 2000 to 2002) and the conducive conditions would cause an increase in the occurrence of malaria in the epidemic-prone areas as was the case in Kabale in 1998 when it last occurred. I had witnessed the epidemic in Kabale in 1998 and this was a window of opportunity of which I wanted to take advantage.

iii. There is little information about cerebral malaria in the highland areas of Uganda and Africa as a whole and a study of this kind would shed some light on this topic.

iv. The workload at the district hospitals, though huge, is not a hindrance to additional research work especially since many of the staff have not been for refresher courses and are keen to acquire new skills and knowledge on the management of the diseases in their communities. My assumption was that they be more motivated to participate in the study and consequently collect better quality data

v. There would be some benefit to the patients since medication and some equipment was to be provided for the management of cerebral malaria as part of the study. Supplies of such items are sometimes erratic at the district level

and the assistance from the study would help to save lives in this way. Any skills which the staff acquired during the study could then be utilised for other purposes

vi. Follow-up and tracing of survivors would be easier to arrange and conduct with the District Health Services who could provide personnel and vehicles for this purpose. The public health structure at district level is well defined making it easier to arrange for the follow-up of survivors using the already established links.

With these in mind, four district hospitals were used in the multi-centre design. The possibility that the sample size might not be achievable in one year (i.e. two rainy seasons) at the four sites was not neglected. In such a situation the contingency plans were to a) include a fifth site, or b) extend the enrolment phase of the study to one more rainy season, or both.

The study was to cover many aspects of patient management and as a result it was necessary to collaborate with other researchers on malaria in Uganda. Upon returning to Uganda, I visited several researchers to find out in what ways they could assist me in preparing the study. As a result, a number of collaborative links were established which will be highlighted in the course of this thesis.

The study was divided into three phases, a *Pre-recruitment phase* (April 2001 to 31 December 2001), *Recruitment phase* (1st January 2002 – 31st December 2002 then extended to July 2003) and *Follow-up phase* (February 2002 to August 2003). Each phase involved specific activities conducted by the Principal Investigator (PI) and collaborating institutions. The key activities that were performed in each phase include the following:

3.3.1 Pre-recruitment phase

i. Development of the data collection tools *Checklist 1* and *2*, *Forms 1, 2, 3*, and *4*.
ii. Development and adaptation of case management tools.
iii. Development of training materials for the study teams.
iv. Selection of study teams comprising of laboratory, nursing and clinical staff.

v. Training the study teams to use the data collection tools and to follow the management and evaluation guidelines.

vi. Piloting of data collection tools to determine their suitability and eliminate errors.

vii. Identification of deficiencies in the routine triage of patients and finding solutions to speed up diagnosis and treatment.

viii. Identification of deficiencies in the provision of medication and sundries required to manage cerebral malaria at the study hospitals.

ix. Putting in place systems to supplement any deficiencies that were identified and those that developed during the study period.

x. Obtaining clearance from various organisations to carry out the study.

xi. Procurement of study supplies and equipment from within and outside Uganda.

xii. Linking up with other malaria scientists within the country and to make them aware of the study.

xiii. Development of a tool for assessing cognitive function in survivors during follow-up.

3.3.2 Recruitment phase

i. Enrolment of cases that met the selection criteria.

ii. Management of cerebral malaria cases according to the study guidelines.

iii. Informing other health units, both government and non-government, within the catchment areas of the study hospitals. I looked through their records and how they managed severe malaria. Those without the capacity to manage cerebral malaria were encouraged to refer suspected cases to the study hospital as quickly as possible (including arranging transportation if required which would be paid for by the study).

iv. Maintaining a register of all admissions of malaria at the study hospitals.

v. Maintaining a record of all supplies provided to the study hospitals.

vi. Validating laboratory results and implementing quality control measures.

vii. Maintaining a bank of frozen sera at the study sites.

viii. Training new team members when there were routine changes of staff.

3.3.3 Follow-up phase

i. Assessing survivors for neurological deficits. This occurred simultaneously with case enrolment.

ii. Tracing subjects who do not attend follow-up visits on schedule.

3.4 Study Sites

One consideration in selecting the sites was the need to use areas in which the age spectrum of subjects with cerebral malaria was wide enough to elucidate the influence of age-of-onset on disease. A number of areas were considered and were visited by the Principal Investigator in July 2000. The epidemiology of malaria is influenced by the level of malaria transmission so much so that the severe forms of malaria are more prevalent in the under 5 year olds than in those above in areas with moderate to high transmission. As the level of transmission declines, the occurrence of severe malaria shifts towards the older age groups whenever such a population is exposed to malaria for example during an epidemic. This background was taken into account when selecting the study sites. In describing the study areas, special attention is given to factors such as rainfall and altitude which influence the degree of malaria transmission. Table 3.1 provides some geographical and climatic characteristics of the areas visited.

Each facility was assessed to determine its suitability for the study. To make the process of selection systematic a "suitability score" was constructed and used to score each hospital. For each parameter assessed, see Table 3.2, each hospital got a score of zero for poor, one for good and two for very good. The table gives the scores each hospital obtained for each parameter. I realise that this assessment was based upon personal observations during one visit. The completeness of the data was not certain and data depended heavily on the diagnostic criterion used at each site, as well as the accuracy of diagnosis.

Table 3.1: Summary of the physical and climatic characteristics of the towns in which possible study hospitals are situated.

Town/District	Malaria endemicity	Altitude (metres)	Mean annual rainfall (mm)	Mean annual minimum temperature (degrees C)	Mean annual maximum temperature (degrees C)
Kabale	Hypoendemic	1,830 – 2,130	890 – 1,020	10	25
Kisoro	Hypoendemic	1,830 – 2,130	1,520 – 1,780	7.5	22.5
Masaka	Mesoendemic	1,220 – 1,520	1,140 – 1,270	15	27.5
Mbale	Hyperendemic	1,220 – 1,520	1,270	15	30
Tororo	Hyperendemic	1,070 – 1,220	1,397	15	30
Kapchorwa	Hypoendemic	1,830 – 2,130	1,905	12	27.5
Apac	Holoendemic	760 – 1,070	1,397	17.5	30

Table 3.2: Parameters of the suitability score that were used to select hospitals for the study on the neurological sequelae of cerebral malaria.

Parameter	Kabale	Mutolere	Masaka	Kisoro	Mbale	Tororo	[illegible]	Apac
More than 50 recorded cases of cerebral malaria per year	0	1	2	0	2	2	*	0
Laboratory facilities to perform basic investigations	1	2	0	0	2	0	0	0
Adequate number of clinical staff to attend to admitted patients	1	0	1	0	2	0	0	0
Adequate number of nursing staff to attend to admitted patients	2	2	0	0	1	0	1	0
Clinical staff who are interested in collaborating	2	2	1	0	1	1	1	1
Conditions suitable for disease in a wider age group	2	2	0	2	1	0	2	0
Total score	8	9	4	2	9	3	4	1

* No records available for assessment

Three of the hospitals selected, Kabale, Mutolere and Mbale ranked highest on the suitability score. Kapchorwa hospital which was also selected did poorly on the scale but could not be left out because it is in a malaria epidemic-prone area. Four hospitals were therefore selected for the multi-centre study. The following paragraphs give a succinct account of the four study hospitals and the districts in which they are located.

3.4.1 Mbale District

Mbale district is situated in the Eastern region of Uganda. It is bordered by Kenya to the East, Tororo to the South West, Kumi to the North West and Kapchorwa to the North East. The district lies at altitudes between 1,299m and 1,524m above sea level. The average annual rainfall reaches up to 1,191mm. The population of the district according to the 2002 population and housing census is 720,925 (50% males). The main economic activities are agricultural based *viz.*, subsistence farming of maize, beans, cassava, bananas, soya beans, yams, rice, and coffee; and rearing of cattle, goats and sheep (GOU. 2004d).

The district is unique because close to Mbale town is Wanale ridge which is at an altitude of about 2,270m above sea. The area is very fertile and has its own unique vegetation and eco-system. The people that live there are mostly farmers and regularly take their produce down to the markets in Mbale town.

Mbale district has one regional hospital, Mbale hospital; one district hospital, Bududa hospital; seven health centres; twenty-eight health centres; seventy-four health units and twelve first aid posts at village level. There are 438 staff employed in the health sector and they include health inspectors, health assistants, health educators and health visitors. 500 community resource personnel like traditional birth attendants (TBAs), community council aids, and peer educators. Some of these workers have been trained in health education and home visiting. They participate in outreach programmes, TB case tracing and immunisation. Malaria is the number one cause of morbidity and mortality in the district. The district has a few control measures in place and plans to implement more. Two entomologists are responsible for overseeing vector control strategies like barrier spraying (although the supply of insecticides is erratic) and destruction of mosquito breeding sites. Pregnant women

and HIV infected/AIDS patients are given prophylactic chloroquine. Insecticide treated bednets are to be acquired and a mechanism to distribute / impregnate them at a subsidised price is being formulated. The Director of the District Health Services (DDHS) overlooks all the health issues of the district.

3.4.2 Mbale Regional and Referral Hospital

Mbale hospital offers clinical and outreach services to the population of Mbale. Its catchment area extends over the entire Eastern region which is a combined population of 6,301,677 people. The hospital has two surgical wards, and three medical wards of which one is for children aged 12 years and below. The hospital has an ample number of specialists and medical officers. Two consultant paediatricians run the children's ward and one consultant physician is responsible for running the adult medical ward. There is an ophthalmology and physiotherapy unit. The laboratory is fairly well-equipped with staff consisting of two senior lab technologists, one senior lab technician and a few lab assistants.

3.4.3 Kapchorwa District

Kapchorwa district is located in the Eastern region along the slopes of Mt Elgon (summit at 4,932m). The mountainous terrain lies between 1,500m and 3,000m above sea level. Annual rainfall ranges between 920 and 1,650mm. The duration and timing of the two rainy seasons varies with altitude whereby the higher the altitude, the longer the rains. Kapchorwa has a population of 193,510 people (50% male), is served by 1 Government hospital and 26 Health centres of various levels of sophistication. The infant mortality rate in the district was estimated to be 104 deaths per 1000 livebirths slightly less than the estimated national figure of 122 deaths per 1000 livebirths (time period for this calculation was not given). The main cash crops grown are maize, bananas, coffee, beans, wheat, and sunflower (GOU. 2004b).

Malaria was not a major public health problem in the district but over the past few years it has become a big killer. The District Health authorities attribute this to warmer climatic conditions and the massive deforestation that has been going on in the district, see Picture 1.

Picture 1: A picture of the landscape in Kapchorwa district showing the large areas of forest that have been cleared for farm land (Taken by James Tibenderana in 2003).

3.4.4 Kapchorwa District Hospital

Kapchorwa hospital is a 100 bed facility. Its staff include three MOs, five clinical officers, ten nurses and ten midwives, one lab technician and two lab assistants. The hospital serves a population within the district though its catchment area includes the south part of Moroto district and the eastern parts of Kenya. Complicated cases that cannot be appropriately dealt with at the hospital are referred to Mbale hospital, a distance of about 60km on a recently completed all season road. There are outpatient services such as general care, antenatal care, immunisation and Sexually Transmitted Infections (STI). Basic investigations are performed at the small laboratory. A small records unit is manned by one records clerk.

3.4.5 Kabale District

Kabale is situated in the south-western region. It is surrounded by Rukungiri to the north, Kisoro to the west, Ntungamo to the north east and Rwanda to the south. Average annual rainfall is between 1,000 and 1,480mm. The district is very hilly and the altitude is between 1,219 to 2,347m. It has a population of 471,783 people (46%

male). Farming is the main form of livelihood. Crops grown include potatoes, sorghum, beans, and peas (GOU. 2004a).

The district has a weekly surveillance of five diseases, namely malaria, polio, cholera, dysentery, and measles. All the 46 health units in the district report the frequency of these diseases to the office of the Director of DHS. This surveillance system was put in place after the malaria epidemic in the south western parts of Uganda in 1998. Malaria control activities are reinforced in areas that record surges in malaria cases. These activities include household and barrier spraying when the insecticide is available, destroying the mosquitoes' breeding sites and ensuring that there is an adequate amount of chloroquine at the nearest health centre. Health educators and sanitation teams are dispatched to these areas when the need arises. Another way by which they monitor the prevalence of severe malaria in the community is by the demand for blood transfusions at the district hospital.

3.4.6 Kabale Regional and Referral Hospital:

Kabale Hospital is a district and referral hospital situated in Kabale Municipality, about 400km from Kampala. The hospital has a capacity of 250 beds and its referral facilities serve a combined population of about six million inhabitants. It offers clinical services, surgical and medical; and outreach programmes such as immunisation and family planning.

The hospital has two paediatricians (consultant and registrar) two surgeons (surgical and obstetric), one physician and two Medical Officers. The hospital has a few nurses who carry enormous workloads. The lab is manned by two senior laboratory technologists. Like all hospitals in the country, a record of all inpatients and outpatients is kept. Basic information on each hospital attender is recorded.

3.4.7 Kisoro District

Kisoro, in the south western tip of Uganda, like Kabale is very hilly. It is at the border with, Rwanda to the South and the Democratic Republic of Congo to the West. The climate is similar to that of Kabale with an average annual rainfall of 1,600mm. The altitude ranges between 1,200 and 2000m above sea level. The district has a population of 219,427 people (45.2% male). Agriculture is the main

economic activity in the district. It is one of the least developed districts in Uganda and has poor road infrastructure (GOU. 2004c).

3.4.8 St. Francis Hospital, Mutolere:

Mutolere Hospital is a missionary hospital that is run by the Kabale Diocese of the Church of Uganda. It is located in about 11km from Kisoro town and has a capacity of 220 beds. It offers only clinical services and is not a referral hospital. However because of inadequate medical services at Kisoro hospital (it has now been renovated), the only other hospital in the district, and the poor road network to Kabale (56km away) most patients have to go to Mutolere for their health needs.

Two consultants, a gynaecologist and paediatrician, and two medical officers run the hospital. The hospital has a nursing training school. An assistant laboratory technician runs the small but well stocked laboratory. Most basic laboratory investigations are carried out there. The hospital records were fairly well kept and up-to-date

Like all missionary hospitals in the country, patients have to pay user fees for the health care they receive. Though a minimal fee, these charges can be substantial if a family is large and its members are sick many times in a year. Those who cannot meet the charges are either given waivers or allowed to pay the charges at a later date. Arrangements were made with the hospital administration not to charge patients who were admitted with cerebral malaria during the study period. The costs of their treatment were to be paid by the study.

3.5 Study population

The population from which cases were selected resided in areas with moderate to low malaria transmission at the time when they were admitted to hospital. These areas were at altitudes above 1,200 metres. They had to be resident within the catchment area of the study hospital. Inclusion and exclusion criteria (incorporated in *Eligibility Checklist 1* and *2*) were employed to choose study cases from consecutive patients admitted with impaired consciousness due to non-traumatic causes. The attributes used in the selection process include those given by Warrell *et al* to differential patients that match the case definition for cerebral malaria from

other unconscious patients (reference here). Other attributes such as age and residence, were employed to choose a group that could be assessed reliably with the study tools and was from within the catchment area of the study hospital (WHO 2000). Below are the inclusion and exclusion criteria.

3.5.1 Inclusion criterion

A patient who was admitted to any of the study hospitals was enrolled into the study if all of the following were present:

i. Aged between 12 months and 70 years at the time of admission.
ii. Has impaired consciousness characterised by inability to localise painful stimuli or unawareness of the environment.
iii. Has the specified level of consciousness above for a minimum of thirty minutes in the case of a child (below 10 years) and one hour in the case of those 10 years and above.
iv. Has fever or convulsions, or a history of fever or convulsions, within the last week preceding admission.
v. Has a positive blood smear for *P. falciparum*.

3.5.2 Exclusion criterion

On the contrary, a patient with any of the following was not enrolled into the study:

i. Has had an accident or knock on the head which has caused the current loss of consciousness.
ii. Has evidence of other encephalopathies like bacterial meningitis.
iii. Is a known epileptic with more than 3 convulsions in the last six months preceding admission.
iv. Has evidence of any physical deformity that will compromise neurological assessment.
v. Has evidence of any neurological deficit preceding the current episode of coma.
vi. Resides more than one day's travel to the hospital by whatever means of transportation used to get to the hospital.
vii. Is known to be pregnant at the time of admission.

3.6 Case definitions

Cerebral malaria was defined according to the WHO definition in which a patient is considered to have cerebral malaria if he/she

i. is in unrousable coma
ii. has *P. falciparum* parasitaemia
iii. has normal cerebrospinal fluid and
iv. does not have any other identifiable cause of coma.

This definition constitutes a "*definite*" case of cerebral malaria (DCM). *A priori*, an additional definition was agreed to enable the inclusion of cases that either did not have all the features of the strict WHO definition or had altered mentation but not in unrousable coma.. These cases formed a group of "*probable*" cerebral malaria*. The attributes that describe both forms of cerebral malaria in this study are given in Table 3.3. The necessity for these two groups is to combine the strict research definition (DCM) with the more practical one (PCM) and facilitate the enrolment of more cases. Additionally, there is the need to determine whether cases of probable cerebral malaria are on the pathway towards definite cerebral malaria in which case the rapid deterioration to coma necessitates that they are managed as cerebral malaria. Hospitals in Uganda admit patients with life-threatening conditions. With regards to malaria this comprises patients with severe forms of malaria. This group forms the denominator when calculating the proportion of cerebral malaria among falciparum admissions since it was not possible to determine the size of the population from which the cases came from.

* These terms are documented in the literature Brewster, D. R., Kwiatkowski, D. and White, N. J. (1990). "Neurological sequelae of cerebral malaria in children." *Lancet* **336**(8722): 1039-43. Kamble, M. B., Raut, P. P. and Hussain, Z. F. (2002). "Cerebral malaria in rural India." *Indian Journal of Pediatrics* **69**(8): 659-61.

Table 3.3: Attributes that contribute to the definitions of cerebral malaria in the study

		Case Attributes			
Scenario (ranked)	**Altered mentation**	***P. falciparum* asexual forms**	**State of cerebrospinal fluid**	**Blood glucose**	**Definition / remarks**
Child					
1	Unrousable coma for ≥30 minutes	Demonstrable	Aseptic	Within normal range	Definite
2	Unrousable coma for ≥30 minutes	Demonstrable	Not measured but no neck stiffness	Within normal range	Probable
3	Unrousable coma for ≥30 minutes	Not demonstrable but has received quinine within the previous 48 hours*	Aseptic	Within normal range	Probable
4	Unrousable coma for ≥30 minutes	Demonstrable	Aseptic	Not assessed	Probable
5	Unconscious but able to localise painful stimuli for ≥30 minutes	Demonstrable	Aseptic	Within normal range	Probable
Adult					
1	Unrousable coma for ≥ 60 minutes	Demonstrable	Aseptic	Within normal range	Definite
2	Unrousable coma for ≥ 60 minutes	Demonstrable	Not assessed but no neck stiffness	Within normal range	Probable
3	Unrousable coma for ≥60 minutes	Not demonstrable but has received quinine within the previous 48 hours	Aseptic	Within normal range	Probable
4	Unrousable coma for ≥60 minutes	Demonstrable	Aseptic	Not assessed	Probable
5	Unconscious but able to localise painful stimuli for ≥ 60 minutes	Demonstrable	Aseptic	Within normal range	Probable

* No case (child or adult) was included with this scenario

3.7 Study Outcomes

The main outcomes are *mortality* and *neurological sequelae*. Mortality refers to death. Neurological sequelae refer to any neurological deficits that persist beyond the time when the subject has recovered from cerebral malaria well enough to be discharged from hospital. Recovery is judged in terms of regaining consciousness i.e. a score of 5 on the BCS or 15 on the GCS. A neurological deficit refers to a problem with brain or nerve function that affects either a specific ability or a specific location. This study was designed to examine for gross motor and sensory deficits as well as gross cognitive abnormalities. The kinds of deficits that were sought are given in the list below:

Motor-sensory deficits

- Weakness of a limb or limbs
- Abnormal tone as either increased tone or reduced tone
- Abnormal gait or the inability to walk in an individual who could walk before the bout of cerebral malaria
- Tremor or tremors
- Cerebral palsy
- Epileptic fits
- Blindness
- Inability to vocalise properly in a child who could do so before
- Cranial nerve deficits such as facial nerve palsy
- Hearing loss
- Persistent headache
- Dizziness

Cognitive deficits

- Memory impairment
- Attention deficit disorders
- Restlessness
- Hallucinations
- Aggressive behaviour
- Personality changes
- Depression

The main outcome measures that were used for analyses were:

i. The proportion of cases that died of cerebral malaria among the cases of cerebral malaria admitted during the study period.

ii. The proportion of cases that developed one or a combination of neurological sequelae among survivors that attend examination.

3.8 Protocol Development meeting

A protocol development meeting was held in Kampala on 22nd August 2001. Twenty-two participants comprising some members of study teams from the four hospitals and other malaria researchers attended, see Picture 2 for a group photo taken at the end of the meeting. The main reasons for this gathering was for participants to get to know each other, for the principal investigator to explain the study, for participants to agree management guidelines, laboratory evaluations and monitoring procedures, to clarify procedures for obtaining informed consent and HIV testing, and to find ways of cooperating between study sites and other researchers in the country. The case record forms were reviewed and changes suggested to make them more adaptable to the local settings. Additional tools were suggested which the principal investigator was to develop.

Picture 2: Group photograph taken at the end of the Protocol Development meeting held on 22nd August 2001 in Kampala.

3.9 Data collection tools

The study was conducted in a clinical setting at four sites that are far apart. None of these sites had been involved in a clinical study before. Much of the data required was of a routine nature but needed to be collected in a structured and uniform manner. To do this, data collection tools that were appropriate for the setting were needed. Several kinds of tools were used to extract data and data collection. Below is a description of these tools.

3.9.1 Case record Forms

I visited Kemri/Kilifi, in Kenya, in July 2001 to see how they had organised their studies on cerebral malaria. I obtained copies of their case record forms (CRFs) and adapted them with permission before returning to Uganda to prepare the ground for this study. I presented the adapted copies at the Protocol Development meeting and several changes were suggested by the participants. To take on the suggestions, I had to redesign the forms paying particular attention to the following requirements:

i. **Clarity** – The forms were written in English since this is the official language in Uganda. However it is not the first language for most people, more so at a district hospital in a semi-rural environment where the staff are used to communicating in the local languages. The instructions and questions therefore had to be phrased in sentences with little or no ambiguity.
ii. **Easy to complete** - The additional burden of collecting these data had to be minimised so that team members were co-operative. To do this, the CRFs needed to be easy to complete with well sequenced questions so that one did not have to jump from one page to the other and back again. Instructions on how to carry out the various examinations needed to be on the forms even at the expense of the length of the questionnaire.
iii. **Separate tools for each level of patient management** – Since it was agreed that case management would be levelled with different cadres of staff participating, each CRF had to be tailored to fit the level at which it would be used. Therefore *Eligibility checklist 1* and *Form 1*, which were completed by the nurse-on-duty had to contain questions that reflected the nurse's duties and

knowledge whereas *Eligibility checklist 2* and *Form 2* which were completed by the Medical Officer contained more technical terminology.

iv. **Uniform data quality** – This was a multi-centre study and consequently, team members needed to understand the questions in similar ways and respond as accurately yet as consistently as possible. To achieve this, closed-ended questions were used where possible. A combination of dichotomous and multiple-choice responses were provided. Item check-lists were also employed for example, the *Eligibility checklists 1* and *2*.

v. **Visually appealing** – The forms contained many questions and instructions. Consequently, much care was taken in their layout to prevent the pages from appearing congested. Some forms, for example the observation chart, were printed on coloured paper to be easily identifiable.

vi. **Layout that would allow data to be extracted easily** – The forms were designed so that electronic forms with a similar layout could be designed in MS Access. This would allow data be extracted more easily from the hard copies to the electronic ones with fewer mistakes.

3.9.2 Consent Form

This was a one-paged form that was translated into the local languages that were common in that area. An *Information sheet* that provided a summary of the study was also translated. Copies of the data collection tools, information sheets and consent forms can be found at the end of the end of this document in Appendix I.

3.9.3 Aide memoirs

There was a need to develop *aide memoirs* of guidelines on some aspects of data collection and case management. These would not only serve as reminders to team members but also provide a standard by which all teams had to abide. Posters of the following guidelines were made and placed on all wards, copies of which can be found in Appendix II.

i. **Management of the patient with cerebral malaria** – This was adapted from International guidelines compiled by Warrell *et al.* (1990).

ii. **Evaluations of the patient with cerebral malaria** – This specified chronologically the forms to be completed and the laboratory investigations to be performed.

iii. **How to measure blood glucose using a glucometer** – This gave a step-by-step account of how to use the glucometer provided. None of the hospitals used a portable glucometer routinely. Therefore once the staff were trained how to use the glucometer, there was a need for such a reminder.

iv. **How to measure blood pressure using an automatic sphygmomanometer** – An automatic BP machine was provided to each ward. This was a new piece of equipment and to facilitate its use, step-by-step instructions were compiled onto a poster and placed on a visible part of the ward.

3.9.4 Piloting of data collection tools

The data collection tools were piloted at Mbale hospital between 1 and 31st December 2001. Thirteen patients who were suspected to have cerebral malaria were recruited and managed. Six cases during this same period were managed at Kapchorwa hospital and used to pilot the data collection tools and streamline patient triage procedures. Completed forms were reviewed to determine any amendments that needed to be made to the tools, recruitment procedures, triage or management methods. Some errors were noted and appropriate corrections made. Final copies of the tools were printed and distributed to study sites based on these amendments. It was not possible to pilot the tools at all four study sites during the same period because of the availability of patients fitting the selection criteria. Cases matching the selection criteria did not attend the other two hospitals until much later. It was decided to use the first five or so cases that were admitted at these two hospitals when ever they became available to try the data collection tools and get the study teams familiar to them and the data management guidelines. Five cases met the selection criterion of *Checklist 1* at Kabale hospital between April and July 2002. These were the initial cases admitted to that hospital that appeared to have cerebral malaria. They were used to pilot the data collection procedures and tools. Similarly two cases were used to pilot study materials at Mutolere hospital. *Form 5* which was developed in the course of the study was not piloted.

3.10 Data collection procedures

At all study hospitals, the major participating units were the paediatric and medical units. Patients who were deemed to be suitable for the study were triaged according to procedures that were put in place by the study teams and PI. Management was

staged in to five levels to enable different kinds of data be collected by different cadres of staff over the period of time during which the subject was on the ward. In this manner, the responsibilities of care and data collection were distributed over different personnel and over time reducing the additional burden that a study of this nature places on already busy staff. The stages of case management were assigned five levels as:

3.10.1 Level One

Initial case selection was conducted by the admitting nurse, who completes *Eligibility checklist 1* within 2 hours of the patients admission to the ward. Nurses are usually the first contact that a patient has at most hospitals in Ugandan. This is due to the relative scarcity of doctors at hospitals *vis-à-vis* the large number of admissions. The nurse took a history using a structured questionnaire, *Form 1* and determined among others a) if the patient could localise pain, b) the concentration of blood glucose using a glucometer and c) body temperature. A thick smear of blood is made and sent to the laboratory to determine the presence of *P. falciparum*.

3.10.2 Level Two

A second check was carried out within 6 hours by the Medical Officer who filled in *Eligibility checklist 2*. This assessment takes into account the results of laboratory investigations such as a blood smear and random blood sugar which may have been performed after the nurses assessment. Cases who met the requirements at this level continued into the study. Those who did not, stopped contributing information to the study but continued to be managed according to the guidelines laid out. Those who were eligible underwent a detailed clinical examination conducted by the Medical Officer who completed *Form 2*, see Picture 3.

Picture 3: A Medical Officer in Kapchorwa hospital examines one of the study patients in Level 2 (Taken by James Tibenderana, 2003)

3.10.3 Level Three

At Level 1 a thick smear for screening is carried out on all patients that fulfilled the *Eligibility checklist 1*. Those with a preliminary positive smear were further evaluated according to a defined protocol in which a number of confirmatory investigations are done. These include thick and thin blood smears, random blood glucose, CSF analysis, full haemogram, and urinalysis. A specimen of serum was stored and dried blood spots made. These procedures constituted Level 3 and all data collected were entered into *Form 3*. Repeated measurements of vital signs, depth of coma and parasite density were performed to monitor each case's progress and recoded on the *observations chart*. A study nurse was responsible for obtaining consent from survivors when they had regained full consciousness. Those who gave consent for their data to be used for the study proceeded to the next level, Level 4.

3.10.4 Level Four

Once a survivor regained consciousness, the study doctor carried out the first detailed neurological assessment of the subject. *Form 4* contains structured examination questions. It was used at this level to extract information about the neurological status of the case. When the subject has completed a seven-day course of quinine, he/she is discharged if the blood smear is clear of asexual forms of Plasmodia on a minimum of two consecutive occasions 24 hours apart. A date for the first follow-up visit is given and the subject discharged. This constituted Level 4.

3.10.5 Level Five

The final stage of data collection and case management was Level 5. During this stage each patient is invited for two visits one month apart to have a detailed neurological assessment. Assessments are performed by a study doctor. *Form 5* is used to extract the required information. Motor-sensory deficits were sought. Cognitive function was also assessed using a primitive tool that was developed for the study. Unfortunately due to time and financial constraints, only a simple attempt was made to test the validity of the cognitive tool in the study setting.

3.11 Case management

The management of a cerebral malaria case involved treatment (definitive and ancillary), nursing and supportive care, laboratory evaluation, and follow-up. For cases from the hospitals to be similar with respect to survival it was imperative that the care that they received was uniform at all the study sites. For this purpose, time was spent developing protocols for case management which study teams would follow. Below is a list of which were used.

Table 3.4. Guidelines for the Management of the Cerebral Malaria Patient

1. Ensure that the patient has a clear and patent **airway**
2. Place the patient in the **semi-prone** position, changing sides every 4 hours
3. Do a quick but thorough **examination** and determine the depth of coma.
4. Take a **thick smear** to confirm *P. falciparum* parasitaemia.
5. Do a **blood glucose** estimation with the stix method
6. Weigh the patient if possible
7. Start **quinine** therapy in 5% dextrose (use a volume of 10ml/kg for a child and 200mls for an adult patient). The regimen of quinine is:
   (a) **Loading dose** of 20mg/kg over 4 hours if the patient has not received quinine in the preceding 48 hours
   (b) **Maintenance dose** of 10mg/kg over 4 hours given 8hourly. (If it is not possible to set-up an IV line, then give the quinine dose as a deep IM injection and give the dextrose via an NGT, then set-up the IV line)
   (c) Start on an oral dose of quinine as soon as the patient can swallow. Give 10mg/kg of quinine orally. Observe the tablets being taken.
   (d) Treat the patient with quinine for 7 days ensuring that the patient receives the full course.
   (e) Reduce the dose of quinine by 1/3rd if the patient is unconscious for more than 3 days
8. If the patient is **hypoglycaemic** with a blood glucose equal to or less than 2.2 mmol/L, give 1ml/kg of 50% dextrose IV (diluted to make twice the volume) over 5 minutes before commencing quinine therapy. Give 10% dextrose infusion at 4ml/kg/hr. Repeat the blood glucose measurements after 1 hour. If the blood glucose is still low then repeat the treatment above until the patient improves.

Table continued overleaf

Table 3.4 continued

9. If the patient has **repeated convulsions** lasting more than 10 minutes. control them with diazepam. Give:

(a) Child – Diazepam 0.15mg/kg slow IV injection

(b) Adult – Diazepam 10mg slow IV injection

Alternatively, diazepam can be given via the rectal route in subjects over 10kg at a dose of 0.5mg/kg (do not combine with rectal paracetamol). Treatment can be repeated after 30 minutes to control further convulsions.

10. If the patient has a **fever** (axillary temperature above 38.5°C) give paracetamol orally if the subject can swallow. Give

(a) Child – Paracetamol 90mg/kg/24 hours given 4 or 6 hourly

(b) Adult – Paracetamol 1g given 6 hourly

If the subject is vomiting give the same dose via the rectal route (but do not combine with rectal diazepam).

11. Treat **severe anaemia** (Hct < 15% or Hb < 5 g/dL) with a transfusion of packed cells at a dose of 10ml/kg. If packed cells are not available then use fresh whole blood at a dose of 20ml/kg.

12. If the subject is in **shock** (systolic blood pressure < 50mmHg in children 1-5 years or < 70 mmHg in older subjects) give an appropriate dose of crystalloids.

13. If there is a suspicion of **bacterial meningitis**, administer appropriate antibiotic cover suited to the local sensitivity patterns. A stiff neck and strong focal neurological signs like a facial nerve palsy and dense hemiplegia are suggestive.

Table continued overleaf

Table 3.4 continued

14. Perform a **lumbar puncture** as soon as this is possible. Do not carry out an LP if:

(a) Glasgow Coma Scale is 6 or less

(b) Blantyre Coma Scale is 3 or less then 3

(When the score improves the LP can be performed)

(c) there is papilloedema on fundoscopy

(d) there was a history of projectile vomiting, headache and impaired vision

15. Perform further **laboratory investigations** specified in the study protocol and any others related to the associated medical problems.

16. Take repeated **observations** as specified below.

Parameter	**Frequency**	
	Unconscious phase	**Recovery phase**
Axillary temperature	6 hourly	12 hourly
Pulse and Blood pressure	6 hourly	12 hourly
Respiratory rate	6 hourly	As required
Level of consciousness	6 hourly	At discharge
Blood glucose	6 hourly or more frequently if there is hypoglycaemia	
Parasite density	Daily and at the completion of treatment	

17. **Discharge** after the completion of 7 days on quinine treatment when the blood smear is negative for falciparum parasites and the subject has regained full consciousness (i.e. scoring 14 and above on the Glasgow Coma Scale or 5 on the Blantyre Coma Scale). Make sure that the subject is able to feed properly.

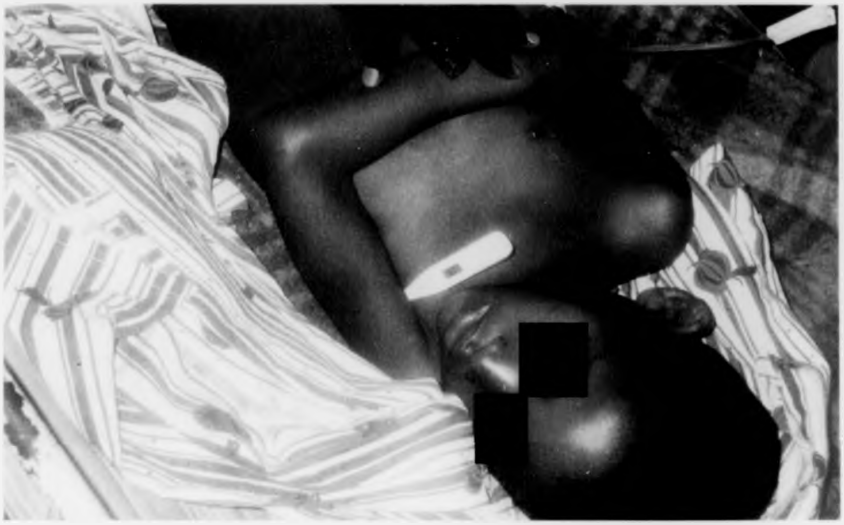
3.11.1 Treatment

It was agreed that quinine would be given as the definitive form of treatment starting with a loading dose of 20ml/kg body weight for those who had not received quinine within the preceding 48 hours then 10mg/kg body weight 8 hourly for a total of seven days. This dosage is that recommended by Warrell in his supplement on the Severe and Complicated Malaria (Warrell, Molyneux *et al.* 1990). A shorter course for five days was combined with Fansidar® (locally available brand of SP) when the patient could not tolerate the full course. To facilitate compliance, survivors were kept on the ward for seven days and observed swallowing their tablets*. Treatment commenced with IV quinine and was followed with oral quinine as soon as the patient could take orally. It was vital that quinine was started early and it was agreed that the nurse-on-duty could begin treatment without waiting for the doctor to prescribe as long as the guidelines were adhered to. To ensure that the quinine given was good quality, all cases received quinine which was procured by the Principal Investigator from the Joint Medical Stores (one of the two medical stores that procure essential drugs on behalf of the MOH for its health facilities). All other medication were also obtained from the same unless not available there. All medication was given free-of-charge.

3.11.2 Nursing care

The nursing of an unconscious patient is intensive. The guidelines clearly stated what needed to be done and nurses revised and practised how to carry them out before the study started. While the patient was unconscious, the depth of coma was monitored by determining whether he/she could localise a painful stimulus. This simple test could be performed by the nurses. A portable glucometer was used to monitor blood glucose while an automatic BP machine was used to measure blood pressure and pulse. Fever was measured with digital thermometers, see Picture 4.

* Nurses had reported that they suspected mothers were saving some tablets intend for the sick child for their other child. This they thought occurred when the sick child had improved but was still getting oral medication.



Picture 4: A comatose child whose axillary temperature is being measured with a digital thermometer (Taken by James Tibenderana, 2003)

3.11.3 Laboratory evaluations

Cases were evaluated in a systematic manner according to a protocol which was developed with the study teams, see Appendix II Activities such as laboratory evaluations were specified by the day from admission, i.e. Day 0 represented the day of admission and Day 7 represented seven days since admission This schedule only served as a guide and some events could occur later or earlier than stated in the *aide memoir* The procedures used in carrying out some of the laboratory evaluations are standard ones as described by Cheesebrough (1998) and are outlined in Appendix III

3.11.4 Informed Consent

A senior nurse administered the *Information sheet* to the adult subject in the presence of a relative then sought consent from the subject In the case of a child, who in Uganda is legally defined as one who is less then 18 years, consent is sought from the next-of-kin Consent was obtained for two activities; (a) to include the

subject in the study and (b) to carry out HIV-1 serology on a stored sample of blood. A subject could agree to be included in the study but refuse to have HIV serology. Alternatively a subject could agree to both in which case he/she can decide whether he/she would like to be given his/her result. The next-of-kin was asked to provide consent for patients who do not survive. This was done before the relatives leave the hospital.

3.11.5 Support

Physiotherapists, Ophthalmologist and occupational therapists participated in case management when required and when available. Unfortunately, district hospitals do not always have these cadres of staff. The study doctors offered as much support in this case by giving appropriate advice or referrals.

3.11.6 Follow-up

During the follow-up period survivors were treated for any ailments they had when they came for their visits. A transport refund was given to them at each visit. In Kapchorwa district, those who did not turn up for their appointed visits were visited at home by one of the study nurses and requested to attend follow-up at the study hospital. A full clinical and neurological assessment was carried out. Fundoscopy was performed; visual acuity tested; and an audiometer used to test hearing. Cognitive function was assessed with the tools developed (see section 3.12). As was the practice I saw at Kilifi, subjects were given a mug of tea containing sugar (with or without milk according to preference) and sugar-containing biscuits before they underwent the examination. This was done to minimise the effect of a low blood glucose (hunger) on cognitive function. It also enabled the young subjects to be less nervous about the examination. Staff did not wear clinical attire to make the session less of a clinical interaction. Young children were assessed on a floor mat if the assessor felt it would make the child more cooperative.

3.12 Development of tools for cognitive assessment

A number of tests of cognitive function were considered. None of them appeared to be useable for the assessment of survivors (Berch, Krikorian *et al.* 1998; Bogousslavsky and Fisher 1998; Fisher 2001). I sought advice from the two clinical neurologists at Mulago Hospital on how to adapt the tests to suit the local setting in the country. With their advice, *Form 5* was developed to assess for cognitive functions such as memory, language, comprehension and expression.

3.12.1 Child version of cognitive tool

A combination of questions and tasks were employed to examine cognitive function in children aged 3 years and above. Mothers (or the person who usually lives with the child) are asked about some aspects of the child's behaviour before and after the episode of cerebral malaria, see RC in *Form 5*. The child is asked to carry out some simple instructions such as naming common objects (cup, spoon, comb, plate, pencil and plastic container used to keep water, locally called a jerry can) and what they are used for. These objects were supplied solely for the assessment and all study hospitals had similar objects. Each child is also asked to carry out simple tasks like putting a spoon in a cup. In this manner language and verbal comprehension was assessed. Memory was assessed by asking the child to point at six objects laid out in a set pattern after the assessor had shown the subject what to do, see MEM in *Form 5*. An object was then hidden away and the subject asked to find it and return it to where it was. For each task a score of 1 was given if it was carried out correctly and 0 if otherwise. A maximum of three attempts were allowed without prompting.

The consultant paediatric neurologist and I used these cognitive tools to assess 29 children that had been attending the neurological clinic at New Mulago Hospital. A study nurse trained to use the tools assessed 21 children in Kapchorwa town at their homes. Table 3.5 below summarises the characteristics of both groups.

Table 3.5: General characteristics of neurological cases and controls used in the trials of Form 5.

Characteristic	Known neurological cases (n=29)	Controls (n=21)†	P-value / Remark
Median age (years)	6 years (range 2-11)	5 years (range 2-8)	0.139
Ethnic groups	Ankole, Teso, Ganda, Soga	Gisu, Kikuyu, Nandi, Sabiny	Come from different ethnic groups
Proportion who go to school	55% (n=11)	52% (n=16)	0.845
Modal level of education of mother	Completed primary school (7 mothers)	Educated up to 4th year at secondary school (7 mothers)	Level higher in mothers of controls
Median score for items found at home‡	5 (range 2-10)	4 (range 1-12)	0.593
Median number of siblings	3 (range 0-9)	2 (range 1-6)	0.311

Cases and controls differed in the composition of their ethnic groups and the level of education of mothers. Neither of these factors are known to be related to cognitive deficits in the communities. The median score for items owned a proxy measure for socioeconomic status was larger among cases than controls but this was not significantly different ($p>0.05$). The children version of the cognitive tool consisted of six instructions to carry with each instruction in turn consisting of six questions. A score of one was given if the question was carried out successfully and zero if it was failed (within three attempts). The scores for the neurological cases and their controls are given in Table 3.6. As shown there variation in scores between both groups was not large. One instruction language and verbal comprehension 2 had different distributions between cases and controls. Controls all scored six on language and verbal comprehension 2 whereas cases scored between zero and six.

In the memory section of the tool, neurological cases and controls had a median score of 3 on memory instruction 2 but controls had about half the variance in their score compared to cases.

† Group matched by age of controls
‡ Proxy measure of socio-economic status

Table 3.6: The scores obtained in a trial of a questionnaire to determine differences in cognitive function between cases and controls.

Instruction	Median scores on first attempt (range; variance)		P-value
	Cases (n=29)	Controls (n=21)	
LGVC1	6 (0-6; 2.0)	6 (0-6; 2.0)	0.918
LGVC2	6 (0-6; 1.8)	6 (6-6; 0)	0.015
LGVC3	6 (0-6; 4.0)	6 (3-6; 0.9)	0.963
LGVC4	6 (0-6; 6.5)	6 (0-6; 4.5)	0.446
LGVCtotal[§]	24 (0-24; 47.3)	24 (11-24; 14.2)	0.637
MEM1	3 (0-5; 5.2)	5 (0-5; 4.6)	0.219
MEM2	3 (0-3; 1.7)	3 (0-3; 0.8)	0.071
MEMtotal[¶]	6 (0-8; 11.2)	8 (0-8; 7.9)	0.143

Having known the results from the trial of the child version of the cognitive tool in neurological cases and controls an attempt was made to calculate the sensitivity and specificity of the various instructions of the tool. The scores were considered in two age groupings, children aged 1 to 4 years and those between 5 and 10 years, since it was very likely that the ability to perform the instructions could be associated with age in a broad sense. A number of cut-off scores[††] were assessed using Receiver Operating Characteristic curve (ROC curves) to determine the proportion of neurological cases with cognitive dysfunction that were correctly identified by the instruction. Table 3.7 lists the sensitivities and specificities for a selection of cut off scores for instructions of the cognitive tool divided into those aged under 5 years and those aged 5 years and above.

The cut-offs that were selected for use in the study were language and verbal comprehension 2 equal to 5 or less, language and verbal comprehension total equal to 18 or less, and memory total equal to 6 or less. The cut offs that were able to identify a higher proportion of cases with cognitive dysfunction among the two age groups were used which were those with the higher sum of sensitivity and specificity. This approach was used to screen for children likely to have cognitive dysfunction and was not a confirmatory tool.

[§] Total score obtained by adding the scores for LGVC
[¶] Total score obtained by adding the scores for memory
[††] Higher scores indicate better performance

Table 3.7: Receiver Operating Characteristics (ROC) of a selection of cut-off scores of a questionnaire tried on children with known neurological deficits and community controls .

Instruction	Sensitivity %	Specificity %	Correctly classified (%)	ROC area
Aged less than 5 years (16 observations)				
LGVC1 score				0.48
<=0	0	100	44	
<=5	22	71	44	
LGVC2 score				0.21
<=0	100	0	56	
<=4	0	43	19	
<=5	**100**	**0**	**44**	
LGVCtotal score				0.36
<=11	67	29	50	
<=18	**33**	**43**	**38**	
<=22	11	71	38	
MEM2				0.29
<=0	100	0	56	
<=2	33	29	31	
<=3	22	43	31	
MEMtotal				0.33
<=0	100	0	56	
<=6	**33**	**57**	**44**	
Aged 5 years and above (31 observations)				
LGVC1 score				0.51
<=2	100	0	39	
<=5	8	95	61	
LGVC2 score				0.42
<=3	100	0	39	
<=4	0	84	52	
<=5	**0**	**100**	**61**	
LGVCtotal score				0.43
<=15	17	74	52	
<=20	8	74	48	
<=22	0	84	52	
MEM2				0.39
<=0	100	0	39	
<=1	0	100	61	
<=3	0	79	48	
MEMtotal				0.40
<=0	100	0	39	
<=6	**0**	**79**	**48**	

3.12.2 Validation child version of cognitive tool

An attempt was made to validate the cognitive tool. There was no gold standard test or combinations of tests that have been used in Uganda to identify cognitive deficits in children or adults. To validate the current tool, the only available option was to assess children clinically for cognitive deficits. This was done by reviewing their medical records at the neurological clinic. The paediatric neurologist examined the records (consisting of clinical notes made at regular visits at the outpatient neurology clinic) of thirty children to determine whether they had any cognitive deficits by the date of their most recent visit and if so, to grade them on a scale of no incapacity (score of 0), mild incapacity i.e. has one deficit that is subtle (score of 1), moderate i.e. has two / three deficits that do not affect daily activities (score of 2) or severe i.e. has a deficit/s that do not allow normal daily activity (score of 3). A questionnaire was used for this purpose. At the time of this exercise the paediatrician was not aware of the scores that the children had gotten on the cognitive tool. The table below, Table 3.8, summarises Kappa statistics results for data from 26 children with scores on the cognitive tool and the paediatrician's review. The paediatrician's expert opinion did show good agreement with some components of the cognitive tool and not with others. Having no better alternative, the cognitive tool was used for the assessment of study cases during follow-up.

Table 3.8: Agreement between the median cognitive scores obtained by a sample of children with neurological dysfunction and their degree (on a scale of 0 to 3) of cognitive incapacity determined by assessment of their case notes by a senior consultant paediatric neurologist

Component of cognitive tool	Age group	Degree of Cognitive Incapacity determined by retrospective review of case records				Kappa Inter-agreement	P value for Kappa
		None	Mild	Moderate	Severe		
Number of subjects	***26***	***14***	***3***	***4***	***5***		
LGVC1	All	6	6	6	6	0.08	0.05
	≤ 5 yrs (n=8)	6	6	-	4.5	0.18	0.01
	> 5 yrs (n=18)	6	6	6	6	0.03	0.28
LGVC2	All	6	4	6	6	0.14	0.01
	≤ 5 yrs	6	4	-	6	0.39	<0.001
	> 5 yrs	6	4.5	6	6	0.03	0.28
LGVC3	All	6	5	6	6	0.17	0.01
	≤ 5 yrs	6	3	-	3.5	0.49	<0.001
	> 5 yrs	6	5.5	6	6	0.05	0.18
LGVC4	All	6	6	6	6	0.25	<0.001
	≤ 5 yrs	2	0	-	6	0.79	<0.001
	> 5 yrs	6	6	6	6	0.05	0.18
LGVCtotal	All	24	20	24	22	0.07	<0.001
	≤ 5 yrs	16	13	-	14	0.18	<0.001
	> 5 yrs	24	22	24	22	0.02	0.001
MEM1	All	3.5	1	5	0	0.45	<0.001
	≤ 5 yrs	1	0	-	1.5	0.82	<0.001
	> 5 yrs	5	3	5	0	0.33	<0.001
MEM2	All	3	1	3	3	0.34	<0.001
	≤ 5 yrs	2	0	-	1.5	0.80	0.001
	> 5 yrs	3	2	3	3	0.19	0.03
MEMtotal	All	6.5	2	8	3	0.40	<0.001
	≤ 5 yrs	3	0	-	3	0.83	<0.001
	> 5 yrs	8	5	8	3	0.24	<0.001

3.12.3 Adult version of cognitive tool

The adult version involved identification and recall of ten pictures of a variety of objects and recall of six digits. The details of how this was done can be found in the adult version of *Form 5* in Appendix I. Copies of the pictures which were used are given in Appendix IV. Children aged ten years and above, that were attending the paediatric neurological clinic at New Mulago were sought to try the tool on. During the trial period only two children came to the clinic meeting the age requirement. Their scores are summarised in Table 3.9.

Table 3.9: Summary scores of two children with known cognitive deficits who attended the paediatric neurological clinic and performed the cognitive assessment diagnostic tool.

Age of child	Number of pictures correctly identified		Number of pictures correctly recalled		Number of Digits correctly recalled	
	1st set of ten	2nd set of ten	1st set	2nd set	1st set	2nd set
13 years	3	4	0	3	0	0
10 years	8	10	8	6	2	0

It was not considered worthwhile to try the tool in community controls since very few known cases with cognitive dysfunction had been assessed and there was already literature about the performance of children on the two components of the tool. The results of adult survivors would be ranked to determine performance.

3.13 Quality control

A study of this nature required adequate attention to quality control. Measures were put in place at the clinical level, in the laboratory and in data entry.

Quality control in the clinical setting: Procedures for the clinical examination and neurological assessments were standardised. Study members were trained before the onset of recruitment on all aspects of data collection. Doctors were repeatedly checked to determine if they were using the GCS and BCS as taught. Items that were needed for conducting the clinical and neurological examinations were uniform for all hospitals i.e. stethoscopes, glucometers, digital thermometers, and ophthalmoscopes. Batteries were changed regularly and calibrations done.

Quality control in the laboratory: The laboratory procedures were standardised and the laboratory staff trained to follow them. They were encouraged to clean and calibrate their equipment regularly. Slides from one laboratory were taken to another laboratory to validate the parasite counts. On one occasion, the laboratory technician from Mutolere hospital spent four days at Mbale hospital to practice staining and identification of parasites because it was not clear why cases with suspected cerebral malaria in Mutolere continued to have smears in which the technician was not finding parasites.

Quality control during data entry: CRFs were examined at intervals by the PI to assess the information recorded. The accuracy of the recorded information was checked and any errors queried. The study teams were informed of errors in order to avoid committing them again. When designing the electronic forms for data entry, limits were set to prevent the entry of implausible values.

3.14 Clinical standards

It was important to maintain uniform clinical standards at all four sites. Good Clinical Practice guidelines were taught to the clinical staff and they were encouraged to abide by them (Hutchinson 1997; ICH 1999).

3.15 Ethical clearance and considerations

A number of ethical issues were taken into consideration when designing and conducting the study. These are highlighted below:

i. **Informed Consent** – The difficulty was to obtain consent at an appropriate time when the condition of the patient was not too worrying to place the next-of-kin in a position in which consent would be unethical to seek. It was decided that consent would be obtained when the patient had regained full consciousness. However a serum sample would be obtained on admission, which could either be used if consent was given or discarded if consent was refused. In this way there would be a sample of blood that represented the situation the patient was in on admission instead of only getting a sample when the patient had regained consciousness at the time when consent could be obtained.

ii. **HIV serology** - HIV testing was carried out on stored sera which were collected from study patients on admission. If a subject preferred to know their sero-status then pre and post-test counselling was arranged on the ward or during follow-up. If a subject did not want to know their sero-status then the results were kept confidential by the PI.

iii. **Confidentiality** - Each study subject was allocated a unique research number. This number was used on each CRF. *Form 1* is the only CRF that contained the name of a subject. Results like HIV serology which required confidentiality were requested using study numbers with no personal identifiers. Other requests were made in the standard fashion using names as the identifier. A log of subjects' names and their research numbers was kept by the PI and a register kept by the nurse-in-charge of the ward.

iv. **Blood samples** - In order to carry out all the necessary haematological investigations and save some sera for future evaluations, a quantity of blood that was both sufficient and ethically appropriate was calculated. On admission 3mls was collected from an adult patient (10 years and above) whereas only 2mls was taken from a child. In this way, patients were not bled repeatedly and neither were unnecessary amounts of blood taken. Daily blood smears were carried out to determine parasite counts. This was stopped after two consecutive smears in which no parasites are counted. A pin-prick blood sample is used for the smear.

v. **Lumbar puncture** - It is routine practice to perform a lumbar puncture in an unconscious patient who is suspected to have a meningoencephalitis or cerebral malaria. There are two exceptions however, (a) when fundoscopy reveals papilloedema, a sign of raised intracranial pressure and (b) when the patient is almost moribund (Glasgow coma score of 6 or less). These exceptions were upheld in this study. Aseptic cerebrospinal fluid is vital in making a definite diagnosis of cerebral malaria. Therefore, study clinicians were facilitated to lumbar puncture all suspected cases unless the above contraindications existed.

vi. **Use of study supplies** - The study provided items that are necessary to investigate and manage a suspected case of cerebral malaria. Most hospitals in Uganda experience shortages of some supplies. Study

supplies were not withheld from a patient who was unconscious and did not meet the eligibility criteria. Supplies were also not withheld from a non-participating patient with a medical emergency who would benefit from their use e.g. a patient in a diabetic coma who required blood glucose estimation.

vii. **Transport refunds** - At each follow-up visit subjects' are provided with a two-way transport refund. This was given to facilitate their travel to hospital and not as an incentive to participate in the study.

3.16 Study site preparation

The following were conducted at all four sites in order to prepare them for the study:

i. **Needs Assessment** – I visited all four hospitals to determine the gaps in terms of staffing, performance, triage, supplies, equipment, knowledge, and skills. I gathered information by direct observation and consultations with clinical, nursing, laboratory and administrative staff. Meetings between staff were also conducted to enable exchange of ideas on what they felt were the gaps and to propose solutions.

ii. **Selection of study teams** – Study teams were selected at each site. They consisted of the following cadres:

   a. Two laboratory staff were selected to perform laboratory evaluations of study cases. Arrangements were made so that they could cover the laboratory 24 hours of the day.

   b. It was agreed that it would be better to allow all the nurses attached to each study ward i.e. the paediatric and adult wards, to participate in patient management and monitoring. This would avoid the situation in which a nurse who is not part of the team does not monitor study cases on the premise that he or she is not a member of the team. Additionally, most wards in question are understaffed and using only a few of them would place even more pressure on the staff.

   c. Three clinicians per ward assisted in the management of study cases according to the protocol. This comprised of a senior clinician and two other members of staff such as a Medical Officer and a Junior Houseman.

iii. **Training** – Having identified that the staff needed up-to-date information about malaria, good clinical practice procedures and how to participate in a research study, I went ahead to arrange training sessions for the staff. Much time, effort and resources were invested in this because of the strict requirement of performing to international standards and ensuring that all four study sites functioned in unison. Training was done in groups as follows:

a. A laboratory training session was held at the Assessment Centre of Mulago Hospital on 3rd of November 2001. It was facilitated by staff of the Haematology Laboratory of Makerere University Medical School in collaboration with Dr Sarah Staedske, who was conducting a study on malaria at Mulago Hospital. The study lab teams spent a day revising quality control in a research lab, making a thick and thin blood smear, staining a thick and thin blood smear with Giemsa stain, malaria parasite count using the WBC technique, malaria parasite identification, and making dried bloodspots on filter paper. Six team members took part.

b. Training sessions were held for the nursing teams at each site. The Principal Investigator facilitated the training sessions and took the staff through general knowledge about malaria presentation, treatment, prevention and control, how to complete the *Eligibility checklist 1* and *Form 1*, how to obtain informed consent, how to measure blood pressure using the automatic blood pressure machine, how to measure blood glucose using a glucometer, how to make a thick blood smear, and how to manage and monitor a patient with cerebral malaria according to the study guidelines.

c. Dr J. Byarugaba (a senior consultant paediatric neurologist) and Dr E. Dumba (a senior consultant neurologist) gave clinical sessions on the neurological assessment of the patient with cerebral malaria. Two sessions were conducted at Mbale hospital, on the 28th (Paediatric) and 30th (Adult) of November 2001. Two clinicians from Kapchorwa attended both sessions. Dr Dumba gave an adult session at Kabale hospital on 4th January 2002. Two Medical Officers from Mutolere Hospital took part. Dr Byarugaba was not able to give the paediatric

session. These visits gave both Senior Consultants from Mulago Hospital, who are also study collaborators, the opportunity to visit the study sites and interact with the study teams.

iv. **Stocking of supplies** - It was vital that patients received appropriate laboratory evaluations and uninterrupted management. To achieve this, it was noted that some items had to be provided to the wards and the laboratories facilitated with reagents and supplies. Some items were procured from the UK and the majority within the country. These facilities and treatments were provided to patients free. Inventory forms were designed to keep record of items given.

   a. The laboratories were facilitated to carry out the following evaluations: Malaria parasite counts using Giemsa stain [GIBCOBRL KaryoMax® Giema Stain, Improved R66 Solution Gurr Lot No 1020344]; Malaria parasite staging and speciation; Glucose estimation in blood and cerebrospinal fluid using the colorimeter method [Glucose GOD-PAP]; Serum separation and storage [Clot Activator Vacuette®]; Urinalysis [Bayer® Multistix 10SG reagent strips for urinalysis]; Fixation and storage of blood slides [DPX mountant, coverslips, frosted slides, microscope slide cases]; and White blood cell counts, total and differential [Neubauer® counting chamber, counting chamber coverslips].

   b. The wards were provided with the following pieces of equipment: ACCU-CHEK® Advantage® Roche glucometer; ACCU-CHEK® Advantage II/Advantage Comfort glucose test strips; Omron® Blood Pressure Monitor HEM-712C automatic with adult and paediatric cuffs; Littmann® Classic II SE/Paediatric Stethoscope; Gowllands® Diagnostic set; Patellar hammer - Adult/Paediatric; Examination torch; and Omron® MC3B digital thermometers.

   c. Pharmaceutical items and sundries were purchased from the Joint Medical Stores which is one of the major importers of essential medical supplies for the whole country. A list of most of the items purchased is given in the Appendix.

v. **Liaising with other hospitals and community leaders** – Contact was made with other hospitals in the district and health centres to let them

know of the study. Staff were requested to refer cases of cerebral malaria to the study hospital. Community and appropriate District leaders were given information about the study. Their permission was sought to carry out the study in their communities or districts as the case may be.

3.17 Data management

Case record forms were kept in plastic folders with the identification number of the case clearly labelled on each. The folders were colour coded by centre i.e. Mbale had red folders, Kapchorwa blue ones, Kabale green ones and Mutolere white ones. Each centre had a numerical code that preceded the subject's identification number. A log containing personal identifiers and study numbers of all cases that were eligible for the study was kept by the PI. A register of all cases seen on the wards with cerebral malaria was kept by the nurse-in-charge. Another log was kept of all cases of severe malaria that were admitted to the study hospitals during the study period by the records unit of the hospital. Other aspects of data management included:

3.17.1 Storage

Case record forms were stored at study site. At regular intervals the Principal Investigator would collect them and keep them at a central location. Before this, he would check them for completeness and any queries on the data were checked. He would then extract basic information from the forms into the enrolment log.

3.17.2 Confidentiality

Data which was entered into the CRFs was only accessible to the study team members. Information on HIV status was not entered onto the CRFs. The laboratory request for HIV testing had the identification number and no personal identifiers. The lab technician would record the results in a log which was passed onto the Principal Investigator, who would then link the results to the subject. If the results were needed for post-test counselling they would be given to the nurse-in-charge of the ward who would be responsible for linking the results to the patient, counselling the patient or next-of-kin and giving the results.

3.17.3 Data entry

Data was entered into MS Access using electronic forms designed by the Principal Investigator. Their layout was similar to the layout of the case record forms to ease data entry and to reduce errors while entering data. Data entry was conducted by one of the Medical Officers (at Kapchorwa Hospital) and the Principal Investigator (in London). The data from the databases was converted into MS Excel files and examined for consistency. Responses were grouped where necessary and coded. Missing values were coded. Responses that were not applicable for that question were coded to differentiate them from missing values. Data documentation involved labelling all variables and values. It was important to document the data because there were many variables per patient. Clinical signs with findings on the left and right sides of the body were recoded separately.

3.17.4 Data cleaning

At each stage of data collection and entry there are sources of mistakes. It was therefore very important to systematically examine the data for various kinds of errors. The following was done:

i. **Missing data**: Single-variable frequency tables of the data were used to search for missing information. The CRFs of cases without complete number of variables or observations were checked to determine why data was missing. Every attempt was made to find the information and when found entered onto a spreadsheet and transferred into STATA or in some instances entered directly into STATA. It was possible to infer the value of some missing variables from the responses of other variables that were inter-related or providing similar information. In the case of a continuous variable such as body temperature, where ten percent or less of cases had information missing, the mean for all observations was calculated and used to impute missing values. Imputing missing values using the mean would have the effect of reducing the variation of the values of the variable with imputed values and this was minimised by not carrying this out when more the ten percent of the data was missing. In the case of the missing values for pulse rate and respiratory rate which were measured repeatedly, the missing value was replaced with the next measurement. If

the next measurement was missing as well then the value was imputed from the mean for that age group. Where it was not possible to find missing information or to assign sample means or if the proportion of missing observations for that variable was greater than 10%, a separate category for missing observations was created and labelled "missing info". This category was useful because a) cases with missing information could constitute a group with unique features, b) it allowed assessment of having information on that variable related to not having it *vis-à-vis* the outcome and c) the direction of bias caused by the missing data could be appreciated. Another reason for using these measures to eliminate missing values was to maintain a constant sample size throughout all analyses.

ii. **Data entry errors**: In some instances, despite all precautions some errors were made while entering information in the electronic forms. Some questions on the electronic forms had 'yes/no' option buttons with the default set to enter 'no' when not entered. This meant that there was no way of differentiating from the databases when the answer was 'no' because the question had a negative response or the question was not answered because the information was not looked for. Fortunately, much of the data is interlinked with some variables feeding their results into each other. By reviewing the CRFs these errors were identified and rectified.

iii. **Appropriate data values**: All categorical variables were checked to ensure that the recorded data values and codes were correct: for example, if there were three options for a value and a fourth one was erroneously entered. Any such errors that were identified were corrected after checking the CRFs and other variables in the datasets that could shed light on the correct response. A corresponding check for values outside the ranges of continuous variables was done. Some ranges are limited by the study: for example, children aged above one year, and others are biologically set: for example, random blood glucose far exceeding 11 mmol/L on a single occasion without any identifiable reason would be implausible. Such out-of-range values that were not supported by other data were re-entered as missing. Outliers were identified using box and

scatter plots. If their values were consistent with other information then they were left as recorded. If however, their values were not supported then they were re-recorded as missing.

iv. **Date and time variables**: Several variables consisted of information on date and time. They were checked to ensure that the information was accurate and that any derived values that were based on a date/time variable corresponded accordingly. Errors occurred because of the failure to make STATA read the date and time variables when converting the MS Access databases into STATA-readable format. These were rectified by exporting the date/time variables into Excel, formatting them and then converting the spreadsheets into STATA readable format.

3.17.5 Data screening

After ensuring that the data were a good representation of the information obtained from all cases, steps were taken to determine other useful characteristics of the data. The distribution of continuous data was assessed to determine their compatibility with a normal distribution. Pictorial assessment was carried out with frequency histograms and kernel density plots.

3.18 Statistical analyses

Statistical analyses were performed with STATA version 8.1. A plan of analysis was decided upon based on the hypothesis and study objectives. Explanatory factors were defined and variables that met the definitions determined. A list of known and potential risk factors was made. Variables that represented these risk factors were determined either by using existing variables or by generating new ones.

New variables were generated by combining other variables that represented similar data. For example, possibility of shock was determined by combining information on systolic and diastolic pressure, state of extremities, and capillary refill time. It was clear that because of the small number of subjects enrolled into the study it was not feasible to use data from many of the variables as they had been collected. Therefore data had to be combined in a logical manner to create variables with larger numbers of observations per group that would allow more robust analyses. Parametric tests were used where possible and non-parametric tests where the

former were not appropriate, such as when comparing medians of two groups with data not normally distributed.

Continuous variables were assessed to determine whether they should be categorised. Categorisation went ahead if i) natural categorises existed that were defined in the study protocol or elsewhere in the literature, and ii) creating groups would enhance the quality of the statistical analyses for example when the distribution of the variable is non-parametric. In instances in which there were no defined groupings, cut-offs were used to create categories of fairly equal sizes. No more than four categories per variable were made.

The definitions of some variables were decided upon at the preparation stage of the study in which case they were similar to those in previous studies. Other variables were defined according to the data they represented as well as how they had been categorised. Table 3.10 illustrates how the outcome/dependent variables were defined and created. The explanatory/independent variables were grouped into a) Demographic and history information, b) Clinical examination on admission, c) In-hospital non-laboratory information d) Laboratory-based information and e) Follow-up information. Table 3.11 provides a list of these variables, with their definitions and how they are categorised. The table also indicates the method used to create each variable, whether directly from the case record forms or as a summary of other variables.

The threshold for "statistical significance" was an alpha level of 0.05 and two-tailed tests were used in calculating P values. The "clinical significance" of observed differences was also taken into consideration even if they did not achieve "statistical significance" (Lang and Secic 1997). Clinically significant differences were those that had important clinical relevance (or usefulness) either because of their large effect (increased or reduced risk by a factor of at least 3).

Table 3.10: Summary of dependent variables, their definitions, data codes and how they were created.

Variable	Definition	Code	How created
1. Outcome of admission at 72 hours after admission	The result of managing the case upon admission to the ward up to 72 hours after; grouped as survived or did not survive	deaths	Included in case record forms (CRFs)
2. Early-onset neurological sequelae	Neurological deficits of a gross nature detectable between recovery of consciousness (i.e. GCS ≥14/15 or BCS ≥4/5) and discharge from the ward	edefs2	Created by combining other variables from the CRFs.
3. Late-onset neurological sequelae	Neurological deficits of a gross nature detectable after discharge up to 45 weeks after discharge.	ldefs	Created by combining other variables from the CRFs

Table 3.11: List of Independent study variables showing their format, definition, code and method used to collect information on them

	Variable (units)	Format	Definition / Comments	Code	Creation*
A	**Demographic and history information**				
1	Centre	Nominal	Study hospital where cases was managed – either Mbale or Kapchorwa	centre	Not created
2	Age (years)	Ordinal	i) Grouped as 1-4yrs, 5-9yrs, 10 & older	agegrp2	Reported
		Ordinal	ii) Grouped as 1-9yrs, 10 & older	agegrp3	
3	Seizures before admission (non-epileptic)	Ordinal	Number prior to admission – grouped as none, 1-3, 4-20.	nseiz24grp	Reported
4	Quinine given before admission (mg)	Nominal	Whether quinine was given within 24 hours prior to admission (No/Yes)	q48	Reported
5	Previous medical admission	Nominal	History of a previous admission for a medical reason with last year (No/Yes)	prevadm	Reported
B	**Clinical examination on admission**				
1	Body temperature (°C)	Ordinal	Body temperature measured in the axilla on admission – grouped as min-38.5, 38.6-39.4, 39.6-42.0	atemp1grp1	Measurement
2	Depth of unconsciousness	Nominal	Able to localise painful stimuli on admission – Level 2 (No/Yes)	loca2	Finding
		Ordinal	i) Depth of coma on admission determined by the score on the Blantyre coma scales – Level 2; grouped as 0-2, 3-5	bcs1grp	Measurement
		Ordinal	ii) Depth of coma on admission determined by the score on the Glasgow coma scale – Level 2; grouped as 3-8, 9-12, 13-15	gcs1grp	Measurement
3	Anaemia	Nominal	Presence of moderate to severe anaemia defined by a Hb concentration of less than 10 g/dL and or the clinical suspicion of moderate to severe anaemia on examination at Level 2 (No/Yes).	anemia	Summation
4	Jaundice	Nominal	Presence of jaundice on clinical examination –Level 2 (No/Yes)	jaun2	Finding
5	Dehydration	Nominal	Clinical finding of moderate to severe dehydration on examination at Level 2	dhydr1	Finding
6	Pulse rate (beats/min)	Ordinal	Number of beats per minute – grouped as 50-84, 85-119, 120-154, 155-max	pul1grp	Finding

Table continued overleaf

* Manner used to collect information that allowed creation of the variable: Reported-Information was given by the attendant; Finding-Information was obtained during history taking or clinical examination; Measurement-Information was measured either once or several times; Derived-Information was calculated; Summation-Information was summarised from a collection of other variables.

Table 3.11 continued

	Variable (units)	Format	Definition / Comments	Code	Creation†
7	Pulse pressure (mmHg)	Ordinal	Difference between systolic and diastolic pressure – Level 1; grouped as 20-39, 40-79	pulpress1grp	Derived
8	Shock	Nominal	Presence of shock as defined by cold extremities with abnormal capillary refill, and or a pulse pressure of 20 mmHg or less (Likely/Unlikely)	shock2	Summation
9	Respiratory rate (breaths/min)	Ordinal	Number of breaths per minute – grouped as 10-29, 30-49, 50-max	rr1grp	Finding
10	Respiratory abnormality	Nominal	Any respiratory abnormality such as irregular rhythm, shallow or deep breaths, respiratory distress, or abnormal breath sounds (No/Yes).	respabnorm	Summation
11	Respiratory distress	Nominal	Likelihood of respiratory distress defined clinically by flaring of nostrils and chest indrawing (Likely/Not likely).	rdistress	Summation
12	Presence of extra heart sounds	Nominal	Presence of extra heart sounds such as added sounds and murmurs on clinical examination	hearts2	Summation
13	Organomegaly	Nominal	Presence of enlarged spleen or liver on clinical examination at Level 2 (No/Yes).	organo1	Finding
14	Spleen size (centimetres)	Nominal	i) Presence of enlarged spleen (No/Yes)	spleen2	Finding
		Ordinal	ii) Size of spleen; grouped as Not enlarged, 2-3, 4-5	spleen1grp	Measurement
15	Liver size (centimetres)	Nominal	i) Presence of enlarged liver (No/Yes)	liver2	Finding
		Ordinal	ii) Size of liver; grouped as Not enlarged, 2, 3-5	liver1grp	Measurement
16	Muscle tone changes	Nominal	Changes in muscle tone of upper and lower limbs at Level 2	tone1	Finding
	Changes in tendon reflexes	Nominal	Changes in the tendon reflexes namely biceps, triceps, knee jerk and ankle jerk, at Level 2	reflexes1	Finding
17	Neck stiffness	Nominal	Presence of a stiff neck at Level 2 (No/Yes)	necks1	Finding
C	**In-hospital non-laboratory information**				
1	Seizures (non-epileptic)	Ordinal	i) Number witnessed during first episode of seizure activity while on admission – grouped as none, 1-3, 4-20.	nseiz2grp	Finding
		Nominal	ii) Presence of seizures while in hospital (No/Yes).	seizure1	Summation
2	Seizure stoppage time (days)	Ordinal	Duration between the date of onset of seizures and date after which there are three days without any visible seizure activity – grouped as 1-2, 3-max	seizstop1grp	Derived

Table continued overleaf

† Manner used to collect information that allowed creation of the variable: Reported-Information was given by the attendant; Finding-Information was obtained during history taking or clinical examination; Measurement-Information was measured either once or several times; Derived-Information was calculated; Summation-Information was summarised from a collection of other variables.

Table 3.11 continued

	Variable (units)	Format	Definition / Comments	Code	Creation‡
3	Total Seizure stoppage time (days)	Ordinal	Seizure stoppage time plus the number of days prior to admission during which the patient reportedly had seizures – grouped as 1- 2, 3-max.	totalseiztimegrp	
4	Fever clearance time (days)	Ordinal	Number of days between date of admission and date when the body temperature is 37 °C and below for two consecutive days – grouped as 1, 2-3, 4-max.	temptime1grp	Derived
5	Total fever clearance time (days)	Ordinal	Fever clearance time plus the number of days prior to admission for which the patient reportedly had a fever – grouped as 1-4, 5-6, 7-20.	totalfevtimegrp	Derived
6	Coma recovery time (days)	Ordinal	Duration between date of admission and date when fully conscious – grouped as 1-2, 3-4, 5-max.	comatime1grp	Derived
7	Total coma recovery time (days)	Ordinal	Coma recovery time plus the number of days prior to admission for which the patient was reportedly unconscious – grouped as 1-2, 3-4, 5-max.	totalcomatimegrp	Derived
8	Quinine given (mg)	Nominal	Whether a loading dose of quinine was prescribed (No/Yes)	qbolus	Finding
		Ordinal	The total amount of quinine prescribed for the first day of treatment (includes loading dose); grouped as <570, 570 and above	qdaily1grp	Finding
D	**Measurements on admission and in-hospital**				
1	Random blood glucose (mmol/L)	Nominal	Presence of hypoglycaemia defined as random blood glucose of ≤2.2mmol/L (No/Yes).	hypogly1	Measurement
		Interval	First measurement of random blood glucose – grouped as 0-4.9, 5-6.9, 7-max	bglu1grp	Measurement
2	Parasitaemia (number of parasites per µL)	Ordinal	Parasite count determined on admission – grouped as min-50,000, >50,000.	para1grp	Measurement
3	Parasite clearance time (days)	Ordinal	Duration between day of admission and day when no parasites are detectable on blood smear for two subsequent days – grouped as 1, 2, 3-max.	paraclear1grp	Derived
4	Haemoglobin concentration (g/dL)	Ordinal	Haemoglobin (Hb) concentration on admission as estimated by Sahl's method – Measured in patients who were suspected to have a low Hb concentration; grouped as min-9.9, 10-max.	hb1grp	Measurement
5	White blood cell count (cells per L)	Ordinal	Total white blood cell count on admission – grouped as 2000-4700, 4701-6700, 6701-max.	wbccgrp	Measurement

Table continued overleaf

‡ Manner used to collect information that allowed creation of the variable: Reported-Information was given by the attendant; Finding-Information was obtained during history taking or clinical examination; Measurement-Information was measured either once or several times; Derived-Information was calculated; Summation-Information was summarised from a collection of other variables.

Table 3.11 continued

	Variable (units)	Format	Definition / Comments	Code	Creation[§]
6	Serum sodium concentration (mmol/L)	Ordinal	Sodium serum concentration – grouped as <135, 135-146, >146	sodiumgrp	Measurement
7	Serum chloride concentration (mmol/L)	Ordinal	Calcium serum concentration – grouped as <2, 2-3, >3	calciumgrp	Measurement
8	Serum calcium concentration (mmol/L)	Ordinal	Chloride serum concentration – grouped as <95, 95-105, >105	chloridegrp	Measurement
9	HIV infection	Nominal	Sero-positive for HIV-1 (No/Yes) or known HIV-positive	allhiv	Measurement

[§] Manner used to collect information that allowed creation of the variable: Reported-Information was given by the attendant; Finding-Information was obtained during history taking or clinical examination; Measurement-Information was measured either once or several times; Derived-Information was calculated; Summation-Information was summarised from a collection of other variables.

3.18.1 Descriptive statistics

Categorical variables: Single-variable frequency tables were made to show the distribution of independent and dependent variables among cases. Contingency tables were used to show the frequencies of categorical variables between i) *definite* and *probable* cases (case definition), ii) Mbale and Kapchorwa (study centre), and iii) aged one to nine years, and ten years and above (age group). A second age group of one to four years, five to nine years and ten years and above was employed in some instances to better understand the influence of age. Contingency tables were also used to test the null hypothesis of associations between groups. Fisher's exact test was used for all comparisons because of the small number (5 cases or less) of expected observations in some cells. Variables with associations that were "statistically significant" at the alpha level were noted and were the first variables to be used in the bivariate comparisons as described below.

Continuous variables: Measures of central tendency (means and medians) were calculated for continuous variables (normally and not normally distributed data respectively). The Student's t-test for two samples was used to compare means between groups. This was done when the variances of the two groups were fairly equal. When the variances were different, the t-test for unequal variances was employed. For continuous variables that were not normally distributed the Mann-Whitney-Wilcoxon test was used for comparing medians between two groups. When there was need to compare more than two groups the Kruskal-Wallis test was employed. Correlation analysis between continuous variables used either Pearson's correlation or Spearman's rank correlation.

3.18.2 Analyses involving statistical inference

The next step was to calculate measures of association between the outcome variables and the explanatory variables. This was performed in three stages corresponding to the kinds of outcomes; mortality, early-onset deficits and late-onset deficits. Variables used for these analyses were all in the categorical form.

Univariate associations were examined first. Stratum-specific odds of outcome were determined and used to calculate odds ratios (ORs). P-values were obtained from the Wald test for each comparison and used to determine how likely it was that the

association between the outcome and factor occurred by chance. Univariate analysis was useful in identifying variables that would be used in multivariable analyses.

The crude ORs obtained above were adjusted for age (as a categorical variable) to find out if age influenced the association between factors and outcome. The magnitude of the adjusted OR's were compared with the univariate OR's to determine the size of any differences. This process was repeated separately by adjusting the univariate ORs for study centre and for case definition. When the difference between the crude ORs and adjusted OR was large, then the adjusting variable (age, study hospital, or case definition) was considered to confound that association between the factor and the outcome. The variables which were shown to be associated with age, centre or case definition in the contingency tables were the first to be considered in bivariate analyses.

Multivariable analysis was carried out using logistic regression for the two outcomes mortality and early-onset neurological deficits (separately). Explanatory variables were assessed for colinearity and if any were found to be correlated then the variable with the strongest relationship with the outcome was used. A forward stepwise process was used to develop a model containing risk factors for the outcome (at three stages). The plan of analysis followed a systematic manner. Age was first placed in the model since the study hypothesis related age to outcome. Next, study hospital or case definition were included if they had been shown to be confounding variables. Next, explanatory variables which have already been described as risk factors for the outcome were included one after the other. Each time a variable was added, its P value (from the Wald test) in the model was examined. If its P value was statistically significant at the 5% level it remained in the model. If on the other hand its P value was greater than 0.05 but less than 0.1 then the Likelihood Ratio test was used to compare likelihood ratios of the model without the variable against the model with the variable. If the LR test showed that both models differed significantly at the alpha level of 0.05%, then the variable remained in the model. The LR test was also used to decide whether to leave or remove categorical variables that had more than two levels because these had more than one P value (Wald test) whereas the LR test examined all categories as a unit.

After assessing all known risk factors, other factors which were thought to be related to the outcome were added one after the other starting with those with the lowest P values (Wald test) in univariate analyses up to those with P values of 0.2. Finally, variables which were considered to have clinical significance were then included into the model. If their clinical effect remained then they stayed in the model.

Survival analysis was used to develop a model for late-onset neurological deficits. This kind of analysis was used because it could take in to account the time taken to the detection of deficits. Stratified incidence rates were calculated for children and adults separately. Incidence rate ratios were used to compare the stratum-specific incidence rates for adults and children to determine any differences. Next, hazard ratios were calculated and adjusted separately for age, study hospital and case definition. In this way it was possible to determine whether any of the three factors were confounders for the associations between explanatory variables and late-onset deficits. Finally a survival-based model was developed in the same manner as the logistic models previously described.

Chapter 4

I present the results of the analyses in the next two chapters; divided in to descriptive and analytical results. My approach will be to present most of the results here and provide other supporting findings in the Appendix. As well as mentioning my results in a sequential manner, I will in a few instances elaborate key findings and link them with others in order to make this section easier to read and understand.

4. DESCRIPTIVE RESULTS

Descriptive findings are presented to give an overview of study cases and neurological sequelae. Some objectives of the study are achieved with the findings documented in this chapter.

4.1 Case enrolment

Case enrolment began on 1st January 2002. Mbale hospital was the first site to get patients with features suggestive of cerebral malaria. Kapchorwa hospital followed suit. The other two sites, Mutolere and Kabale hospitals, admitted a few cases at the onset of the study that were used as pilots. By the end of the first twelve months (i.e. after two rainy seasons March-May and September-November), there were insufficient cases meeting the selection criteria to end fieldwork. The decision to continue enrolment and cover one more rainy season was taken. By 31st July 2003, when enrolment at all sites ceased, a total of 158 patients with features suggestive of cerebral malaria and meeting the requirements of *Checklist 1* had been admitted to all four sites. Forty-nine cases were disqualified because they could not satisfy the requirements of checklist 2. The reasons why they failed to do so are listed in Table 4.1. This left 109; cases all were from Mbale and Kapchorwa hospitals. After assessment of the data for accuracy and completeness nine cases with incomplete case record forms were excluded leaving 100 cases with sufficient information for statistical analyses. The findings presented henceforth are from these one hundred cases. No subject refused to participate in the study.

Table 4.1: List of the reasons for which cases who met Checklist 1 were excluded from the study

Reason for exclusion	Number of patients				
	Mbale	Kapchorwa	Kabale	Mutolere	Total
Diagnosis not clear	6	3	3	2	14
No malaria parasites demonstrable on thick blood smear	6	0	5	2	13
Below lower age limit	5	0	0	0	5
Diagnosis not cerebral malaria					
Malaria with hyperpyrexia	3	0	0	0	3
Uncomplicated malaria	2	2	0	0	4
Hyperparasitaemia	2	0	0	0	2
Malaria with hypoglycaemia	2	0	0	0	2
Meningitis	2	0	0	0	2
Typhoid fever	1	0	0	0	1
Taken away by relatives	2	0	0	0	2
Died on admission before examination	1	0	0	0	1
Total	**32**	**5**	**8**	**4**	**49**

4.2 Occurrence and monthly frequency of cerebral malaria

The proportion of cerebral malaria among falciparum malaria admissions (aged 1 to 70 years) during the study period 1st January 2002 to 31st July 2003, was 1.9% (100/5381). It was 1.8% (70/3998) in Mbale hospital and 2.2% (30/1383) in Kapchorwa hospital. By age group, the proportion in Mbale was 1.5% (1-4 yrs, 41/2,708), 4.5% (5-9 yrs, 13/286) and 1.6% (10-70 yrs, 16/1,004); the values for Kapchorwa were 0.8% (1-4 yrs, 5/656), 9.4% (5-9 yrs, 13/139) and 2.0% (10-70 yrs, 12/588).

The monthly frequency of study cases is illustrated in Figure 4.1. The largest number of cases were seen in July 2002. Towards the end of fieldwork the frequency had declined to zero. Figure 4.2 gives the monthly frequency by study centre and by case definition. March, April and June 2002 had the maximum numbers of cases managed at Kapchorwa whereas in Mbale it was July 2002.

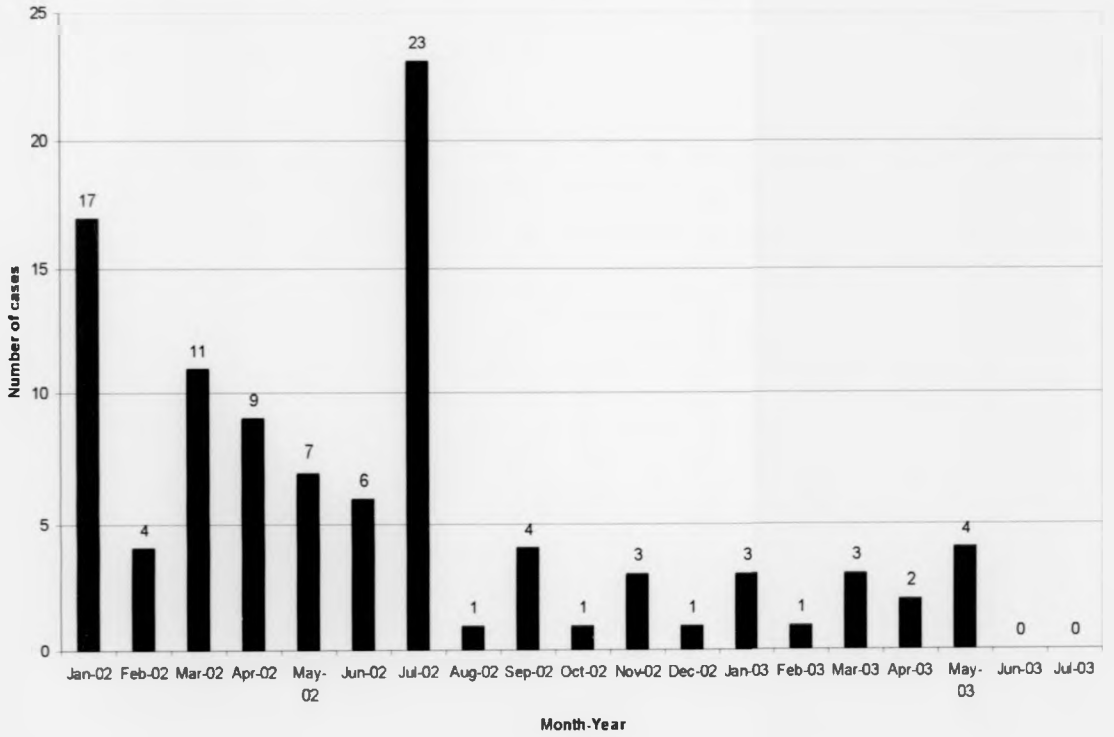
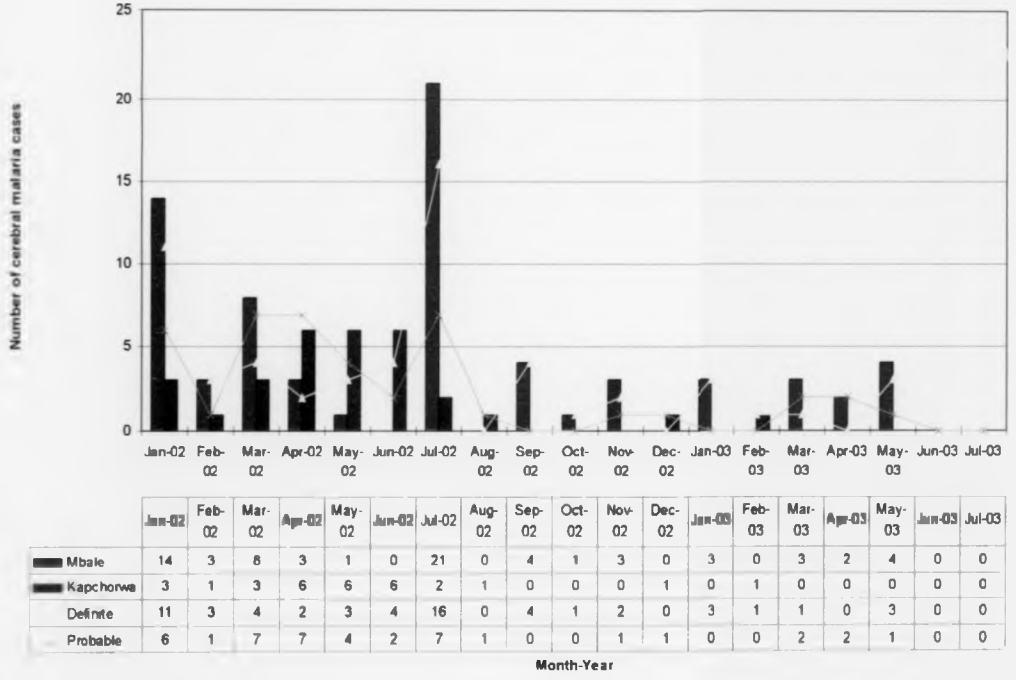


Figure 4.1: Monthly frequency of cerebral malaria cases enrolled at all sites between 1st Jan 2002 and 31st July 2003.



	Jan-02	Feb-02	Mar-02	Apr-02	May-02	Jun-02	Jul-02	Aug-02	Sep-02	Oct-02	Nov-02	Dec-02	Jan-03	Feb-03	Mar-03	Apr-03	May-03	Jun-03	Jul-03
Mbale	14	3	8	3	1	0	21	0	4	1	3	0	3	0	3	2	4	0	0
Kapchorwa	3	1	3	6	6	6	2	1	0	0	0	1	0	1	0	0	0	0	0
Definite	11	3	4	2	3	4	16	0	4	1	2	0	3	1	1	0	3	0	0
Probable	6	1	7	7	4	2	7	1	0	0	1	1	0	0	2	2	1	0	0

Figure 4.2: Histogram of the number of patients with cerebral malaria enrolled into the study between 1st Jan 2002 and 31st July 2003 showing the site to which they were admitted and their case definition.

4.3 Correlation between cerebral malaria and selected weather indices

Historical weather records from the Department of Meteorology, Ministry of Water, Lands and Environment (Government of Republic of Uganda), for the study areas were examined to determine any correlations between selected weather indices and the frequency of cases. Monthly means for rainfall and temperature measurements from periods with continuous information were used. Much of the weather data for the more recent periods was erratic and could not be used for these comparisons. As a result, different time periods and durations were used to determine the mean monthly rainfall and temperature values. Table 4.2 gives a summary of the findings. The calendar year is divided into quarters of three monthly periods to coincide with the two rainy seasons in Uganda.

The mean monthly minimum rainfall measured at Mbale town weather station (altitude 1,153m) between 1908 and 1970 had the highest correlation with case frequency (41%). The information from Sipi and Kapkwata weather stations were used to represent Kapchorwa. Mean total monthly rainfall (measured between 1947 and 1979) had a correlation of 33% with the monthly frequency of cases seen at Kapchorwa hospital

Table 4.2: The correlation between mean monthly measurements of rainfall and temperature as three monthly categories, and the number of cerebral malaria cases seen during a 12-month period.

Mbale	Total rainfall*	Minimum rainfall (mm)	Maximum rainfall (mm)	Daily temperature °C†	Maximum temperature °C	Minimum temperature °C	Number of cerebral malaria cases
December – February	42	0	183	31	37	16	17
March - May	143	29	307	29	35	17	12
June – August	122	49	245	28	32	16	21
September – November	88	15	217	29	34	16	8
Correlation with frequency of cerebral malaria cases	***-0.04***	***0.41***	***-0.14***	***-0.1***	***-0.3***	***0.0***	-
Kapchorwa	**Total rainfall‡**	**Minimum rainfall (mm)**	**Maximum rainfall (mm)**	**Daily temperature °C §**	**Maximum temperature °C**	**Minimum temperature °C**	**Number of cerebral malaria cases**
December – February	47	0	207	25	26	13	5
March – May	189	4	366	24	25	13	15
June – August	209	21	444	22	23	12	9
September – November	175	15	467	23	24	12	0
Correlation with frequency of cerebral malaria cases	***0.33***	***-0.22***	***-0.11***	***0.02***	***-0.04***	***0.28***	-

* Rainfall measurements at Mbale municipal weather station for the period 1908-1970
† Temperature measurements at Mbale municipal weather station for the period 1931-1951
‡ Rainfall measurements at Sipi weather station for the period 1947-1979
§ Temperature measurements at Kapkwata weather station for the period 1979-1985

4.4 Geographic distribution of study cases

Mbale hospital is a district as well as a referral hospital. As a result some of the cases that were managed there lived within the district (45 cases) and others in the neighbouring ones, namely Sironko (14 cases), Pallisa (7 cases), Bugiri, Kapchorwa, Kumi and Tororo (1 case from each). All the cases managed at Kapchorwa hospital were resident in Kapchorwa district.

4.5 General characteristics of all study cases

Explanatory factors were classified into broad groups to reflect the kind of information they represent and the period in patient management when data was collected on them. The broad groups are a) Demographic and history information, see Table 4.3 b) Frequency of symptoms and signs noted during the clinical examination at Levels 1 and 2, see Table 4.4, and c) Frequency of in-hospital features and laboratory-based information, see Table 4.5.

4.5.1 Demography and History information

Fifty-eight cases met the strict definition of cerebral malaria, i.e. unrousable coma due to malaria, as defined in the previous chapter. Forty-two cases were classified as *probable* cases i.e. impaired consciousness due to malaria. Seventy cases were enrolled at Mbale Regional Hospital, which is a large hospital compared to Kapchorwa Hospital where thirty cases were enrolled. The majority of cases (72%) were aged between one (the lower limit) and nine years, with only 28% aged ten years and above. The median age was 6 years (71.5 months) with a range of 1 to 54 years (13-648 months).

Table 4.3: General characteristics of cases enrolled into the study – Demography and History information

Characteristic (N=100)	Measure
A. CATEGORICAL DATA	**Frequency (n)**
Case definition	
Definite	58
Probable	42
Centre	
Mbale	70
Kapchorwa	30
Age grouping 1	
< 10 years	72
≥ 10 years	28
Age grouping 2	
<5	46
5-9	26
≥ 10 years	28
Gender	
Male	55
Female	45
Quinine given within 2 days before admission	38
Antimalarial given in last month before admission*	57
Chloroquine only	50
Quinine only	19
Quinine & chloroquine	12
S/P	2
Previous medical admission	14
Attended follow-up visits	52
B. CONTINUOUS DATA	**Median (range)**
Age (months)	71.5 (13-648)
Duration between discharge and visit (days)	
1st visit (n=53)	33 (2-219)
2nd visit (n=38)	66 (36-276)

* Not including use of quinine in the last 48 hours before admission

The ratio of males to females was 1.2:1. (1:1 for all malaria admissions in the same period). A greater proportion of cases were admitted in the second 6-hour period of the day, i.e. 06:01 – 12:00 hours, as illustrated in the pie chart in Figure 4.3. There was no detectable association between time of admission and outcome (P value was not statistically signifiant). Half of the cases that did not survive were admitted between 12:01 and 18:00 hours (n=5) and 3 fatal cases did not have a record of the time of their admission. All cases that were prematurely taken away were admitted between 06:01-18:00 hours.

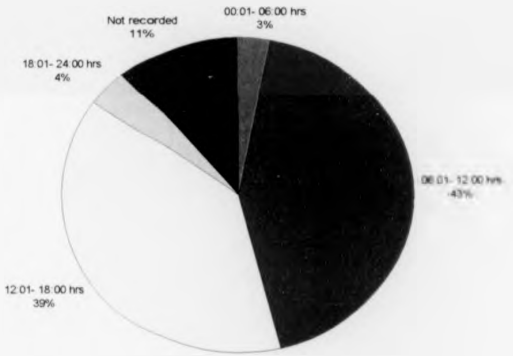


Figure 4.3: Pie chart illustrating the percentage of cases admitted during four 6 hour periods of day

Seventy-six cases had a reported history of seizures in the last 24 hours before admission. Of these, 43 were reported to have had between 1 and 3 convulsions and 33 were reported to have had between 4 and 20 convulsions, see Figure 4.4 for histogram showing the frequency of reported seizures. Twenty-four cases did not have a history of convulsions. Thirty-eight percent of all cases were reported by their attendants to have received quinine within one day before being admitted to hospital. There was an association between having seizures and receiving quinine before admission. Of those who reported receiving quinine, 10% (n=4) did not report convulsions before admission, 53% (n=20) had 1-3 seizures and 37% (n=14)

had between 4-20 seizures (P = 0.04). Referral notes when available were examined to verify information on drugs received.

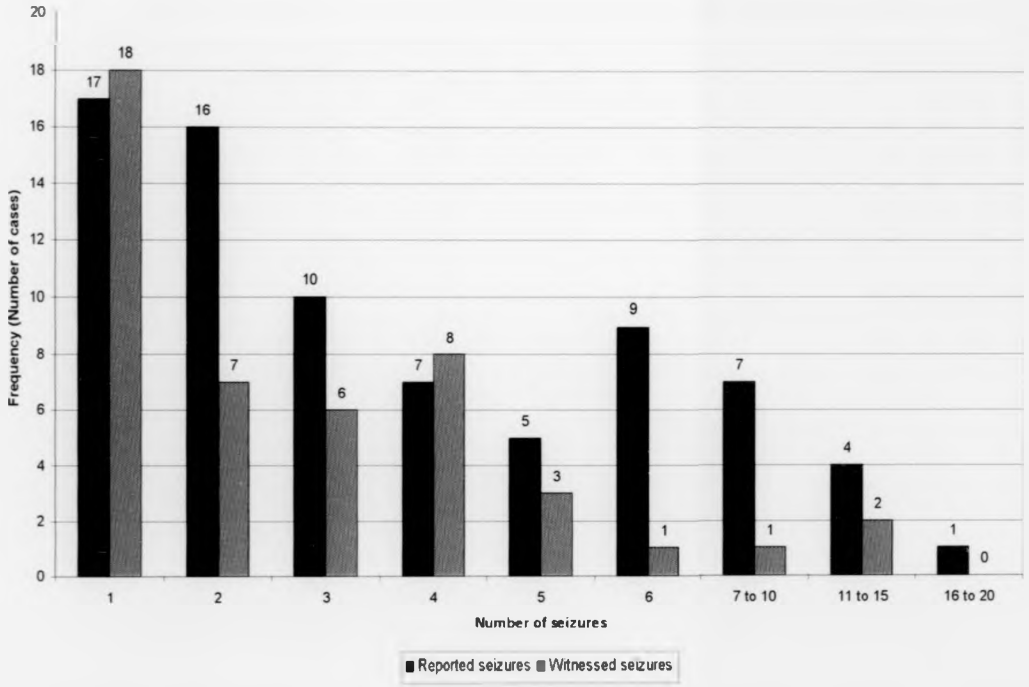


Figure 4.4: The frequency of seizures in cases who either gave a history of seizures within 24 hours before admission (n=76) or had seizures (first episode) while admitted in hospital (n=46)

When attendants were asked about the drugs given to the patient over the last month before admission, 50 reported giving chloroquine only, 19 said quinine only was given, 12 reported giving both chloroquine and quinine and 2 said SP was given. The proportion of cases followed up was 52%, who had a median duration between discharge and the first follow-up visit of 33 days (range 2 to 219 days) whereas the duration between discharge and the second follow-up visit for the 38 cases that attended was 66 days (range 36 to 276 days). Fourteen cases had been admitted to hospital before for a variety of paediatric medical conditions the most frequent of which were febrile illnesses. Of those who were admitted to hospital before, most did not report quinine use in the 24 hours preceding this admission (n=9, 64%).

4.5.2 Frequency of symptoms and signs noted around time of admission (Levels 1 and 2)

Fever was the commonest symptom with 87% of relatives reporting a history of fever. A history of loss of consciousness occurred in 66% while the proportion with confusion, a lesser degree of impaired consciousness, was 56% (some cases having a history of both symptoms). Loss of appetite was reported in 56 cases, headache in 55 cases and vomiting in 42 cases. Cough (39 cases), diarrhoea, rigors and chills (12 cases each) were less frequent. A history of excessive bleeding was not reported as a symptom. These symptoms are not mutually exclusive. At the next stage of management, Level 2, some additional symptoms were noted. Five patients reported having suffered from general body weakness before losing consciousness, two cases lost their ability to speak, and one each, had complained of neck, chest and abdominal pain.

The ability to localise painful stimuli was assessed at Level 1 by the admitting nurse and a few hours later at Level 2 by the admitting doctor. On the first assessment, 52 cases were not able to localise pain whereas on the second assessment this number went up to 75 cases. The depth of unconsciousness was scored on either the Blantyre coma score (in children aged 5 years or less) or Glasgow coma scale (in those aged over 5 years) at Level 2. Thirty-one cases scored 2 or less on the Blantyre coma score (BCS) which corresponds to the inability to localise painful stimuli.

Table 4.4: Frequency of symptoms and signs noted during the clinical examination of cases around time of admission (Levels 1 and 2)

Characteristic (N=100)	Measure
A. CATEGORICAL DATA	**Frequency (n)**
Symptoms documented at Level 1	
Fever	87
Unconsciousness	66
Confusion and unawareness of surroundings	56
Loss of appetite	56
Headache	55
Vomiting	42
Cough	39
Diarrhoea	12
Rigors and chills	12
Excessive bleeding	0
Additional complaints recorded at Level 2	
General body weakness	5
Loss of speech	2
Neck pain	1
Chest pain	1
Abdominal pain	1
Signs noted at both Levels	
Unable to localise painful stimuli on admission*	52
Blantyre Coma Score on admission (excluding 54 cases)	
0-2	31
3-5	10
Not scored with BCS	5
Glasgow Coma Scale on admission (excluding 46 cases)	
3-8	19
9-12	22
13-15	5
Not scored with GCS	8
Body temperature	
35-38.5	63
38.6-39.4	28
39.5-42	9
Moderate-severe anaemia	49
Jaundice	14
Moderate to severe dehydration	8
Pulse rate (beats per minute)	
50-84	21
85-119	34
120-154	37
155-190	8
Systolic blood pressure	
80-99	12
100-119	12
120-139	7
Missing info	69
Diastolic blood pressure	
40-59	9
60-79	19
80-99	3
Missing info	69

Table continued overleaf

* From the Simple tool used at Level 1 by the admitting nurse

Table 4.4 continued

Characteristic (N=100)	Measure
Pulse pressure	
20-39	14
40-79	17
Missing info	69
Shock	5
Respiratory rate (breaths per minute)	
10-29	27
30-49	55
50-89	18
Respiratory abnormality	42
Respiratory distress	5
Extra heart sounds	
No	72
Yes	13
Missing info	15
Organomegaly	35
Spleen size (cm)	
Not enlarged	82
2-3	13
4-5	5
Liver size	
Not enlarged	80
2	6
3-5	14
Muscle tone changes (n=90)	51
Changes in tendon reflexes (n=86)	44
Neck stiffness	10
B. CONTINUOUS DATA	**Mean (95% CI)**
Body temperature	38.1 (37.9-38.3)
Pulse rate	112 (106-117)
Respiratory rate	38 (36-41)
Systolic blood pressure (n=31)	106 (101-110)
Diastolic blood pressure (n=31)	64 (61-68)

Ten cases scored between 3 and 5, and five cases were not scored with this scale despite being 5 years and below. Nineteen cases scored between 3 and 8 on the Glasgow Coma scale (GCS) which represents those not able to localise painful stimuli. Twenty-two cases scored between 9 and 12, and only five cases were found to have mild unconsciousness, i.e. a score of 13-15. Eight cases aged over 5 years were not scored with the GCS despite being in the right age group. Scoring was repeated daily both using the standard scales (BCS and GCS) and by simply determining the ability of the patient to localise painful stimuli. The scores on the first assessment are shown in Table 4.4.

The mean of the first measurement of body temperature (measured in the axilla) was 38.1°C [95% CI 37.9-38.3]. When temperature was categorised, sixty-three patients had temperatures between 35 and 38.5 °C, twenty-eight patients had temperatures between 38.6 and 39.4 °C, and nine had hyperthermia with temperatures between 39.5 and 42.0 °C. Moderate to severe anaemia was present in 49 cases of whom 11 cases also had clinical signs of jaundice. A total of fourteen cases had clinical signs suggestive of jaundice (Level 2). Three cases did not have either clinical or laboratory features of anaemia. Eight children appeared to have moderate to severe dehydration. The first count of the pulse and respiratory rate produced means of 112 beats per minute (95% CI 106-117) and 38 breaths per minute (95% CI 36-41) respectively. The frequency of cases by category of pulse and respiratory rates are given in the table. The pulse rate was imputed in 7 cases using the age-group specific means (as mentioned in the methods, missing values were imputed within categories on which they were not analysed). This was also done for 9 observations without information on respiratory rate. Blood pressure was measured in 31 cases. The mean of the first measurement was 106 mmHg (95% CI 101-110) for systolic pressure and 64 mmHg (95% CI 61-68) for diastolic pressure. The mean of the difference between systolic and diastolic pressure, the pulse pressure, was 41 mmHg (95% CI 37-46). These measurements were categorised, as shown in the table, and included a category for missing values to elucidate if cases with missing information formed a unique group.

The possibility of shock was likely in 5 cases (two cases had pulse pressures of 20 mmHg and in three cases blood pressure was not measured but had other clinical signs of shock). Abnormalities in respiration which included flaring of the alae nasi, use of accessory muscles of respiration, shallow or deep respirations, and abnormal breath sounds were noted in 42 cases. Of these only 5 were likely to have been in respiratory distress because of their extreme features. Extra heart sounds such as added sounds or murmurs were heard in 13 cases and serve as a proxy measure for examination by a doctor since it took some clinical expertise to auscultate and identify added heart sounds. Organomegaly, noted in the form of an enlarged spleen or liver or both was found in 35 cases. Of these the lower margin of the spleen was 2 cm or more below the left costal margin in 18 cases. Similarly 20 cases had palpable liver 2 cm or more below the right costal margin. Nine cases had both an enlarged spleen and liver.

The examining doctor carried out a basic neurological examination on admission. At this time many of the cases were unconscious. 10 cases had a stiff neck and in two of these Kerning's sign was present. Muscle tone changes, either hypotonia or hypertonia, were observed in 51 cases (10 cases were not examined for tone). Hypo or hyper-reflexia of the tendon reflexes (biceps, triceps, knee jerk and ankle jerk) were found in 44 cases out of 86 cases whose reflexes were examined. Thirty-five cases had both changes in tone and reflexes, nine cases were noted to have changes in reflexes but no changes in tone and fifteen cases had changes in tone but no changes in reflexes.

4.5.3 Frequency of in-hospital features and laboratory-based information (Levels 2 and 3)

Following admission, the number of seizures that occurred on the first and subsequent days were recorded. The numbers of witnessed seizures during the first episode (i.e. number of seizures on the first day when seizures occurred) are summarised in Table 4.5. Of the forty-six cases who had seizures (median 2, range 1-11) while on the ward, 31 had between 1 and 3 seizures and 15 had between 4 and 20 seizures, see Figure 4.4. The number of days it took for seizures to be controlled, the seizure stoppage time, was 1 to 2 days for thirty-six cases and 3 to 48 days for ten cases (median for all 46 cases was 2 days, range 1-47).

Table 4.5: Frequency of in-hospital features and laboratory-based information

Characteristic (N=100)	Measure
A. CATEGORICAL DATA	**Frequency (n)**
In-hospital features	
Seizures witnessed (non-epileptic)	
Had none	54
Had any number	46
Number of seizures witnessed (n=46)	
1-3	31
4-20	15
Seizure stoppage time (days)	
1-2	36
3-48	10
Total seizure stoppage time (days)	
1-2	48
3-48	33
No history of seizures or witnessed seizures	19
Fever clearance time	
1	31
2-3	40
4-9	25
Missing info	4
Total fever clearance time	
1-4	39
5-6	32
7-15	29
Coma recovery time (days)	
1-2	25
3-4	33
5-12	14
Missing info or not in coma on admission	28
Total coma recovery time (days)	
1-2	31
3-4	28
5-15	30
Missing info or no history of loss of consciousness	11
Quinine loading dose given on admission	
Not given	76
Given	7
Missing info	17
Dose of quinine given on Day 0	
3-8.9 mg/kg	7
9.0-10.9 mg/kg	19
11.0-20.9 mg/kg	18
Missing info	56
Hypoglycaemia (≤2.2mmol/L)	8
Random blood glucose (mmol/L)	
0.5-4.9	22
5-6.9	26
7-14.9	22
Missing info	30

Table continued overleaf

Table 4.5 continued

Characteristic (N=100)	Measure
Parasite count on Day 0 (parasites/μL)	
100-50,000	52
50,001-595,000	33
Missing	15
Haemoglobin concentration (g/dL)	
3-9.9	38
10-14.9	30
Missing info	32
White blood cell count (cells/L)	
2,000-4,700	25
4,701-6,700	26
6,701-27,000	25
Missing info	24
Serum sodium concentration (mmol/L)	
50-134	33
135-146	20
147-220	8
Missing info	39
Serum chloride concentration (mmol/L)	
80-95	4
95-105	10
106-126	36
Missing info	50
Serum calcium concentration (mmol/L)	
0-1.9	15
2.0-3.0	12
3.1-6.0	26
Missing info	47
Sero-positive for HIV-1	
No	32
Yes	4
Missing info	64
B. CONTINUOUS DATA	**Mean (95% CI)**
Number of seizures prior to admission (median, n=76)	3 (2-4)
Number of witnessed seizures – 1st episode (median, n=46)	2 (1-3)
Fever clearance time (n=78 survivors)	2.8 (2.4-3.2)
Total fever clearance time (n=82 survivors)	5.5 (5.0-6.1)
Coma recovery time (n=67 survivors)	3.5 (3-4)
Total coma recovery time (n=89 survivors)	4.1 (3.6-4.7)
Random blood glucose-geometric mean (mmol/L, n=70)	5.6 (5.0-6.3)
Parasite count-geometric mean (parasites/μL, n=85)	15,973 (9,634-26,482)
Parasite clearance time (days, n=82)	1.8 (1.6-2.0)
Haemoglobin concentration (g/dl, n=68)	9.3 (8.8-9.9)
White blood cell count-geometric mean (cells/L, n=76)	6,046 (5,461-6,695)
Serum sodium concentration-geometric mean (mmol/L, n=61)	127 (121-134)
Serum chloride concentration-geometric mean (mmol/L, n=50)	108 (105-111)
Serum calcium concentration-geometric mean (mmol/L, n=53)	2.2 (1.6-2.9)

The median of the total seizure stoppage time which included the number of days prior to admission for which the case reportedly had fits, was 2 days (range 1-48). Thirty-five cases had histories of seizures but did not have any witnessed ones. The mean fever clearance time was 2.7 days (95% CI 2.0-2.5). The frequency of cases who took one day, 2 to 3 days and 4 to 9 days to clear their fever was 31, 40 and 25 cases respectively. When the numbers of days with fever before admission were added, the mean increased to 5 days (95% CI 4-6). The category-specific frequencies are indicated in the table.

Twenty-five cases took 1 to 2 days to regain consciousness whereas thirty-three cases took 3 to 4 days, and fourteen took 5 to 12 days. The mean coma recovery time (n=72) was 3.5 days (95% CI 3-4) and when the number of days prior to admission for which the patient was reportedly unconscious were added, the mean increased to 4 days (95% CI 3.4-4.5). Seventeen cases with a history of loss of consciousness were not scored on admission and in eleven cases no information was documented on history of loss of consciousness or depth of coma on admission. The minimum total daily amount of quinine prescribed was 225 mg per day and the maximum was 1800 mg per day (this excludes the loading dose). In 19 cases, there was no information in the case record forms of the dose of quinine prescribed. Fifty-two cases were weighed (median 17 kg [95% CI 13-20]) and the amount of quinine given per kilogram body weight per dose (three doses given per day) was calculated for forty-four of these cases as shown in the Table. The mean amount of quinine per unit body weight given as a first dose was 11.4 mg/kg (95% CI 10.4-12.4). Three of the seven cases that received a loading dose of quinine were given 18.8 mg/kg (1 case) and 20 mg/kg (2 cases) as a first dose. It was not possible to determine the dose of quinine given in the remaining four cases.

Hypoglycaemia was found in 8 cases on admission. Twenty-two cases had random blood glucose concentrations between 0.5 to 4.9 mmol/L, twenty-six cases had concentrations from 5 to 6.9 and twenty-two had concentrations from 7 to 14.9 mmol/L. Blood glucose was not measured in 30 cases. The parasite count measured on the first day of treatment (Day 0), ranged from 131 to 590,400 parasites per µL. The mean (geometric) parasite count on Day 0 was 15,970 parasites per µL (95% CI 9,630-26,480); on Day 1 it was 16,050 parasites per µL (95% CI 8,090-31,820); Day

2 it was 2,170 (95% CI 410-11,590) and Day 3 it was 1,540 (95% CI 60-36,840). By the fourth day, all the cases that had parasitaemia on admission had become aparasitaemic. Figure 4.5 shows box plots of the median log parasite count on Day 0 to Day 3 (box borders are the 25th and 75th percentiles and the whiskers represent the lower and upper values). The mean parasite clearance time (n=82) was 1.8 days (95% CI 1.6-2.0). All study cases were positive for *P. falciparum* parasitaemia on the first thick smears carried out on admission as a screening tool. Eighty-five cases had repeated smears to determine their parasite counts on Day 0, seventy-two had repeat smears on Day1, sixty-three on Day 2, forty-three on Day 3, twenty-four on Day 4, ten on Day 5 and 2 on Day 6.

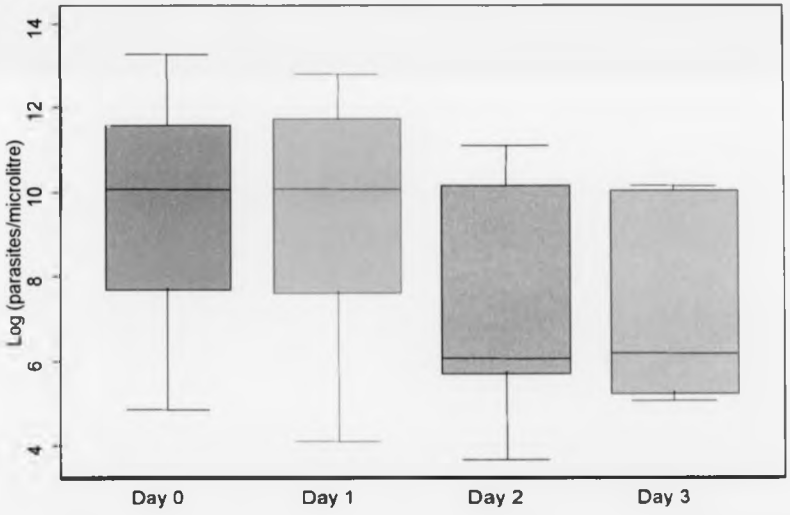


Figure 4.5: Box plots showing the decline in median daily levels of parasitaemia (as log of parasite count) starting with Day 0 (labelled as lgpara1) to Day 3 (lgpara4).

The mean haemoglobin concentration was 9.3 g/dL [95% CI 8.8-9.9]. Thirty-eight cases had haemoglobin concentrations (Hb conc) below 10 g/dL (considered to be the upper limit for anaemia). However, the number deemed clinically to have anaemia was forty-nine because detection of anaemia involved either finding clinical signs such as pale mucous membranes (a commonly accepted method used in Ugandan hospitals) or laboratory detection. White blood cell counts varied widely between 2000 and 27000 cells/L. The mean total white cell count (n=76) was 6,046

(95% CI 5,461-6,695). Four cases (11%) were sero-positive for the Human Immunodeficiency Virus-1 (HIV-1). Initially nineteen samples tested at Mbale hospital were seronegative using ELISA. The stored sera of these 19 cases plus 8 others were retested at the Uganda Virus Research Institute (UVRI) in Entebbe. Two ELISA tests (Murex® and Ani-Labsystems®) were carried out on each sample. Two cases not tested at Mbale had positive results on both occasions. Two cases that tested sero-negative in Mbale had discordant results and the findings had to be confirmed with Western Blot which proved that they were sero-positive[*]. The values of the electrolyte concentrations were not very reliable because of inadequate calibration of the brand new *Vitalab Selectra E analyzer* that was used to analyse the stored sera specimens. As a result of this and the storage process, some of the values are not compatible with the clinical picture of the patients.

4.6 Characteristics of subjects according to case definition

As mentioned earlier in the methodology, cases were divided into two groups according to case definition. *Definite* cases comprised those with the classic definition of cerebral malaria whereas *probable* cases comprised those with lesser degrees of impaired consciousnesses or those who were in unrousable coma but did not have cerebrospinal fluid analysed to exclude meningitis. Comparisons between groups were made to examine if any of the explanatory factors differed greatly between the two groups and to determine if the differences were large enough to take them into account during analyses.

The characteristics of cases by case definition groups, 58 *definite* cases and 42 *probable* cases are summarised in Table 4.6. Mbale hospital contributed 72% (n=42) of *definites* while Kapchorwa contributed 28% (n=16). Of *probable* cases, 67% (28 cases) were seen at Mbale hospital and 33% (14 cases) at Kapchorwa hospital. The case fatality rate was 17% amongst *definite* cases

[*] Three other samples that were collected from patients that eventually were excluded from the study also had discordant results on the ELISA tests done at UVRI. All three were confirmed to be negative with Western blot.

Table 4.6: Characteristics of cases by case definition (N=100 cases)

Characteristics		Definite (n=58)		Probable (n=42)		P-value†
		n	Percentage	n	Percentage	
A. CATEGORICAL DATA						
Demographic & History information						
Centre	Mbale	42	*72*	28	*67*	0.65
	Kapchorwa	16	*28*	14	*33*	
Age grouping 1	< 10 years	44	*76*	28	*67*	0.37
	≥ 10 years	14	*24*	14	*33*	
Age grouping 2	<5	31	*54*	15	*36*	0.22
	5-9	13	*22*	13	*31*	
	≥10	14	*24*	14	*33*	
Gender	Male	29	*50*	26	*62*	0.30
	Female	29	*50*	16	*38*	
Outcome	Survived	46	*79*	36	*86*	**0.002**
	Died	10	*17*	0	*0*	
	Taken away	2	*4*	6	*14*	
Seizures within 24hrs before admission						
	None	11	*19*	13	*31*	0.09
	1-3	23	*40*	20	*48*	
	4-20	24	*41*	9	*21*	
Quinine given before admission		21	*36*	17	*42*	0.68
Previous medical admission		8	*14*	6	*14*	1.00
Clinical examination on admission						
Symptoms at Level 1						
	Fever	50	*86*	37	*88*	1.00
	Unconsciousness	40	*69*	26	*62*	0.52
	Confusion/Unawareness	28	*48*	28	*67*	0.10
	Convulsions	48	*83*	27	*64*	0.06
	Headache	29	*50*	26	*62*	0.30
	Vomiting	29	*50*	13	*31*	0.07
	Loss of appetite	32	*55*	24	*57*	1.00
	Diarrhoea	6	*10*	6	*14*	0.55
	Cough	22	*38*	17	*40*	0.83
	Rigors and chills	20	*34*	13	*31*	0.83
Signs at Level 2						
Unable to localise painful stimuli		57	*98*	18	*43*	**<0.001**
Blantyre coma score on admission (aged ≤ 5 yrs)						
	0-2	27	*84*	3	*18*	**<0.001**
	3-5	2	*6*	8	*47*	
	Not scored with BCS	3	*10*	6	*35*	
Glasgow Coma score (aged >5 yrs)						
	3-8	17	*65*	2	*8*	**<0.001**
	9-12	7	*27*	15	*60*	
	13-15	0	*0*	5	*20*	
	Not scored on GCS	2	*8*	3	*12*	
Moderate-severe anaemia		32	*55*	17	*40*	0.16
Jaundice		8	*14*	6	*14*	1.00
Moderate-severe dehydration		5	*9*	3	*7*	1.00
Pulse pressure	20-39	7	*12*	7	*17*	0.07
	40-79	6	*10*	11	*26*	
	Missing info	45	*78*	24	*57*	
Shock		3	*5*	2	*5*	1.00

Table continued overleaf

† From Fisher's exact test

Table 4.6 continued

Characteristics	n	Definite (n=58) Percentage	n	Probable (n=42) Percentage	P-value‡
Respiratory abnormality	28	*48*	14	*33*	0.15
Respiratory distress	1	*2*	4	*10*	0.15
Extra heart sounds	8	*14*	5	*12*	0.62
Organomegaly	24	*41*	11	*26*	0.14
Enlarged spleen	13	*22*	5	*12*	0.19
Enlarged liver	14	*24*	6	*14*	0.31
Muscle tone changes (n=90)	34	*63*	17	*47*	0.19
Changes in tendon reflexes (n=86)	27	*50*	17	*47*	0.83
Neck stiffness	5	*9*	5	*12*	0.73
In-hospital non-laboratory information					
Seizures – 1st episode					
None	25	*43*	29	*69*	**0.04**
1 – 3 seizures	23	*40*	8	*19*	
4 – 20 seizures	10	*17*	5	*12*	
Attended follow-up	31	*53*	21	*50*	0.68
Quinine loading dose given on Day 0	6	*10*	1	*2*	0.12
Sequelae on discharge at Level 4	15	*31*	8	*19*	0.23
B. CONTINUOUS DATA					
Not normally distributed	**n**	**Median (95% CI)**	**n**	**Median (95% CI)**	**P-value§**
First dose of quinine given (mg/kg)	30	10 (10-11)	14	11 (10-14)	0.89
Age on admission (months)	58	51 (14 – 180)	42	78 (13 – 648)	0.31
No. of witnessed seizures – 1st episode	33	2 (1-3)	13	1 (1-4)	0.74
Seizure stoppage time (n=44 survivors)	31	1 (1-2)	13	1 (1-2)	0.70
Total seizure stoppage time (n=70 survivors)	44	2 (2-3)	26	2 (2-3)	0.70
Fever clearance time (n=78 survivors)	45	3 (2-3)	33	2 (1-3)	0.24
Total fever clearance time (n=82 survivors)	46	5 (5-6)	36	5 (3-7)	0.25
Coma recovery time (n=67 survivors)	43	3 (3-4)	24	2 (2-4)	0.11
Total coma recovery time (n=78 survivors)	46	4 (4-5)	32	3 (2-4)	**0.03**
Normally distributed	**n**	**Mean (95% CI)**	**n**	**Mean (95% CI)**	**P-value¶**
Temperature (°C)	58	38.4 (38.1–38.7)	42	37.7 (37.4–38.1)	**0.005**
Respiratory rate (breaths/minute)	58	43 (39-47)	42	32 (29-35)	**<0.001**
Pulse rate (beats/minute)	58	119 (111-126)	42	103 (94-111)	**0.004**
Systolic blood pressure (mmHg, n=31)	13	105 (97-113)	18	106 (100-113)	0.779
Diastolic blood pressure (mmHg, n=31)	13	66 (59-72)	18	63 (59-68)	0.581
Haemoglobin concentration (g/dL, n=68)	42	9.4 (8.7-10.1)	26	9.2 (8.4-10.0)	0.699
Parasite count (parasites/μL, n=85) Geometric mean	52	13,277 (6,896-25,560)	33	21,374 (9,336-48,933)	0.355
Random blood glucose (mmol/L, n=70) Geometric mean	40	5.8 (5.1-6.6)	30	5.3 (4.3-6.5)	0.473
White blood cell count (cells/L, n=76) Geometric mean	43	6,785 (5,881-7,828)	33	5,203 (4,553-5,948)	**0.03**

‡ From Fisher's exact test
§ From Mann Whitney test
¶ From Student t-test except if the geometric mean was calculated in which case the Mann Whitney test was used

In both groups most were aged less than 10 years (i.e. children), 76% of them *definite* and 67% of them *probable* cases (n=44 & 28 respectively). The median age was 51 months (about 4 years) amongst *definite* cases and 78 months (six and a half years) among *probable* cases. Cases that died after meeting the selection criterion of Checklist 1 were included in the *definite* group resulting in no deaths recorded as *probable* cases.

The symptoms reported by relatives did not vary much between the two groups. Convulsions occurred more often in *definite* cases, 83% (n=48) compared to 64% (n=27) in *probable* cases. This difference was unlikely to be accidental (P = 0.06). Similarly, vomiting was noted more frequently in *definite* cases, 50% (n=29), than in *probable* cases, 31% (n=13) producing a P value of 0.07. The frequency of signs noted by the clinician at Level two were fairly evenly distributed between both groups. Ninety-eight percent (n=57) of *definite* cases were not able to localise painful stimuli, i.e. in unrousable coma. The one case who could localise pain by this stage was already recovering from unrousable coma at Level one.

The first episodes of seizures were noted and the number of seizures grouped as shown in the Table. Twenty-three *definite* cases (40%) had between 1 and 3 seizures and ten (17%) had between 4 to 20 seizures. Eight *probable* cases (19%) had between 1 to 3 seizures and only five (12%) had 4 or more. This difference between groups was significant when compared by categories of number of seizures. As a continuous variable the median number of seizures, excluding those without seizures, was 2 (95% CI 1-3) for *definite* cases and 1 (95% CI 1-4) for *probable* cases. However, the difference in medians was not statistically significant. Fifty-three percent (n=31) of the *definite* cases attended follow-up compared to fifty percent (n=21) of *probable* cases. A similar proportion of *definite* (36%) and *probable* (42%) cases were reportedly given quinine in the 24 hours preceding admission. There was no difference between both groups in the proportion of cases who were hospitalised before this occasion.

The depth of coma was one of the distinguishing (and defining) features between *definite* cases and *probable* cases. As a result, 98% of the *definite* cases were not able to localise pain on admission. When the coma scales were used to determine

depth of coma, the majority of *definite* cases scored lower than the *probable* cases[**]. The proportions of moderate to severe anaemia, jaundice and moderate to severe dehydration did not differ in both groups. The differences in the proportions with respiratory abnormalities, respiratory distress, extra heart sounds and organomegaly between groups were not different (features that could only be identified by a doctor and therefore are proxy measures of the presence of a clinician). Muscle tone changes occurred in 47% of *probable* cases and in 63% of *definite* cases. Changes in tendon reflexes were noted in 50% of definites compared to 47% of *probables*. Neck stiffness occurred fairly equally in both groups.

There was a significant difference in the number of witnessed seizures between groups. The majority of *probable* cases did not have seizures (69%), and of those who did, 19% had between 1 to 3 seizures and 12% had between 4 and 20 seizures. In contrast, 43% of the other group did not have seizures, with 40% having 1 to 3 seizures and 17% having 4 to 20 seizures on the first day when their seizures commenced. Five *definite* cases and 1 *probable* case were given loading doses of quinine although the first dose of quinine, which includes the loading dose, was similar for both groups. Early-onset neurological sequelae were noted at the time of discharge in a greater proportion of *definite* cases (31%) than *probable* cases (19%).

Definite cases had a significantly higher mean body temperature than *probable* cases (38.4 °C [38.1-38.7] compared to 37.7 °C [95% CI 37.4-38.1]). The respiratory rate differed significantly as well, with *definite* cases having a higher rate (43 breaths per minute [95% CI 39-47]) than *probable* cases (32 breaths per minute [95% CI 29-35]). The mean pulse rate in *definite* cases was 119 beats per minute (95% CI 111-126). The same measurement was 103 beats per minute (95% CI 94-11) in *probable* cases. This difference produced a P value of 0.004. Mean haemoglobin concentration was similar in the two groups, 9.4 g/dL (95% CI 8.7-10.) and 9.2 g/dL (95% CI 8.-10.0) in *definite* and *probable* cases respectively. *Probable* cases had a greater parasite count, 21,374 parasites/μL (95% CI 9,336-48,933), compared to *definite* cases, 13,277 parasites/μL (95% CI 6,896-25,560), though the difference was not found to be statistically significant. The random glucose measured at Level

[**] One case aged over 5 years was scored on the BCS instead of the GCS and was not included in these comparisons

1 showed no difference between the two groups. The mean white blood cell count on the other hand differed between both. *Definite* cases had the greater mean white cell count than *probable* cases (P = 0.03).

4.7 Characteristics of cases according to study centre

The characteristics of cases were compared between study centres to determine if there are any differences between study centres in order to take them into consideration during subsequent analyses. Table 4.7 summarises the findings of the comparisons. Of the seventy cases seen at Mbale hospital, 42 (60%) were *definite* and 28 (40%) were *probable* cases. Thirty cases were seen at Kapchorwa hospital of whom 16 (53%) were *definite* and 14 (47%) were *probable* cases.

Seventy-seven percent (n=54) of cases at Mbale were aged less than 10 years whereas sixty percent (n=18) of cases at Kapchorwa were of the same age group. A greater proportion of cases seen at Kapchorwa were 10 years and older (i.e. adults), 40% (n=12), compared to only 23% (n=16) in Mbale (P = 0.09). The median age is also significantly different between the two groups with Kapchorwa cases being older, 8 years (95% CI 6-12), than Mbale cases, 4 years (95% CI 3-6). The case fatality rate at Kapchorwa was higher, 13% (n=4), than Mbale, 9% (n=6). However, the proportion of cases known to have survived at Kapchorwa, 87% (n=26) was higher than at Mbale hospital, 80% (n=56) because it was not known if the 8 cases taken away by relatives survived or not. Assuming that they did survive, then 91% of Mbale cases survived. Seizures before admission were more frequently reported in Mbale (81%) than in Kapchorwa (63%, P = 0.01) with a greater proportion of cases admitted to Mbale (19%) having been previously admitted to hospital.

Table 4.7. Characteristics of cases by centre (N=100 cases)

Characteristics		Mbale (n=70) n	Mbale (n=70) Percentage	Kapchorwa (n=30) n	Kapchorwa (n=30) Percentage	P-value‡‡
CATEGORICAL DATA						
Demographic & History information						
Case definition	Definite	42	*60*	16	*53*	0.65
	Probable	28	*40*	14	*47*	
Age group 1	< 10 years	54	*77*	18	*60*	0.09
	≥ 10 years	16	*23*	12	*40*	
Age group 2	<5 years	41	*59*	5	*17*	**<0.001**
	5-9 years	13	*18*	13	*43*	
	≥ 10 years	16	*23*	12	*40*	
Gender	Male	40	*57*	15	*50*	0.52
	Female	30	*43*	15	*50*	
Outcome	Survived	56	*80*	26	*87*	0.15
	Died	6	*9*	4	*13*	
	Taken away	8	*11*	0	*0*	
Seizures within 24 hours before admission						
	None	13	*19*	11	*37*	**0.01**
	1-3	28	*40*	15	*50*	
	4-20	29	*41*	4	*13*	
Quinine given before admission		26	*37*	12	*40*	0.82
Previous medical admission		13	*19*	1	*3*	0.06
Clinical examination on admission						
Symptoms at Level 1						
	Fever	61	*87*	26	*87*	1.00
	Unconsciousness	50	*71*	16	*53*	0.11
	Confusion/Unawareness	31	*44*	25	*83*	**<0.001**
	Convulsions	54	*77*	21	*70*	0.46
	Headache	30	*43*	25	*83*	**<0.001**
	Vomiting	27	*39*	15	*50*	0.37
	Loss of appetite	30	*43*	26	*87*	**<0.001**
	Diarrhoea	8	*11*	4	*13*	0.74
	Cough	29	*41*	10	*33*	0.50
	Rigors and chills	12	*17*	21	*70*	**<0.001**
Signs at Level 2						
Unable to localise painful stimuli		52	*74*	23	*77*	1.00
Blantyre coma score on admission (aged ≤5 yrs)						
	0-2	27	*63*	3	*50*	0.70
	3-5	9	*21*	1	*17*	
	Not scored with BCS	7	*16*	2	*33*	
Glasgow Coma score (aged >5 yrs)						
	3-8	13	*48*	6	*25*	**0.004**
	9-12	6	*22*	16	*67*	
	13-15	5	*19*	0	*0*	
	Not scored on GCS	3	*11*	2	*8*	
Moderate-severe anaemia		39	*56*	10	*33*	**0.05**
Jaundice		13	*19*	1	*3*	0.06
Moderate-severe dehydration		8	*11*	0	*0*	0.10
Pulse pressure	20-39	6	*9*	8	*27*	**<0.001**
	40-79	7	*10*	10	*33*	
	Missing info	57	*81*	12	*40*	
Shock		5	*7*	0	*0*	0.31

Table continued overleaf

‡‡ From Fisher's exact test

Table 4.7 continued

Characteristics	n	Mbale (n=70) Percentage	n	Kapchorwa (n=30) Percentage	P-value§§
Respiratory abnormality	37	53	5	17	**0.001**
Respiratory distress	5	7	0	0	0.31
Extra heart sounds	11	16	2	7	0.50
Organomegaly	24	34	11	37	0.82
Enlarged spleen	16	23	2	7	0.08
Enlarged liver	16	23	4	13	0.41
Muscle tone changes (n=90)	37	58	14	54	0.81
Changes in tendon reflexes (n=86)	30	47	14	54	0.64
Neck stiffness	5	7	5	17	0.16
In-hospital non-laboratory information					
Seizures – 1st episode					
None	34	48	20	67	0.23
1 – 3 seizures	25	36	6	20	
4 – 20 seizures	11	16	4	13	
Attended follow-up	28	40	24	80	**<0.001**
Quinine loading dose given on Day 0	7	10	0	0	0.06
Sequelae on discharge at Level 4 (n=90)	17	26	6	23	0.79
B. CONTINUOUS DATA					
Not normally distributed		**Median (95% CI)**		**Median (95% CI)**	**P-value§§§**
First dose of quinine given	32	10 (10-11)	12	11 (10-12)	0.95
Age on admission (months)	70	48 (36-68.7)	30	96 (72-142.5)	**0.001**
No. of witnessed seizures – 1st episode (n=46)	36	2 (2-3)	10	1 (1-4)	0.39
Seizure stoppage time (n=44 survivors)	34	1 (1-2)	10	1.5 (1-2)	0.79
Total seizure stoppage time (n=70 survivors)	49	2 (2-3)	21	2 (1-3)	0.29
Fever clearance time (n=78 survivors)	53	3 (2-4)	25	2 (1-3)	**0.04**
Total fever clearance time (n=82 survivors)	56	5 (4-6)	26	5 (3-6)	0.36
Coma recovery time (n=67 survivors)	44	3 (3-4)	23	2 (2-4)	0.95
Total coma recovery time (n=78 survivors)	54	4 (3-5)	24	3 (2-5)	0.73
Normally distributed		**Mean (95% CI)**		**Mean (95% CI)**	**P-value†††**
Temperature (°C)	70	38.1 (37.8-38.4)	30	38.1 (37.7-38.6)	0.81
Respiratory rate (breaths/minute)	70	40 (37-43)	30	35 (30-40)	0.11
Pulse rate (beats/minute)	70	113 (106-120)	30	110 (100-119)	0.63
Systolic blood pressure (mmHg, n=31)	13	103 (96-109)	18	108 (101-115)	0.30
Diastolic blood pressure (mmHg, n=31)	13	66 (61-71)	18	63 (56-69)	0.53
Haemoglobin concentration (g/dL, n=68)	47	9.4 (8.8-10.1)	21	9.2 (8.2-10.1)	0.66
Parasite count (parasites/μL, n=85) Geometric mean	58	12,683 (6,836-23,531)	27	26,215 (10,581-64,956)	0.16
Random blood glucose (mmol/L, n=70) Geometric mean	49	6.2 (5.5-7.0)	21	4.9 (4.0-5.8)	**0.03**
White blood cell count (cells/L, n=76) Geometric mean	51	6,056 (5,326-6,886)	25	6,028 (5,043-7,206)	0.80

§§ From Fisher's exact test
§§§ From Mann Whitney test
††† From Student t-test except if the geometric mean was calculated in which case the Mann Whitney test was used

As expected, fever was the commonest symptom that was reported. It was recorded in the histories of 87% of cases at both Mbale and Kapchorwa hospitals (n= 61 & 26 respectively). Loss of consciousness preceding admission occurred in 50 cases (71%) at Mbale and 16 cases (53%) at Kapchorwa. Confusion was significantly more frequent in cases seen in Kapchorwa (83%) compared to Mbale (44%). Headache (83%) and loss of appetite (87%) were more commonly reported in Kapchorwa hospital than Mbale hospital (43% for each symptom). Vomiting and diarrhoea were as frequent in Mbale cases (39% and 11% respectively) as those in Kapchorwa (50% and 13% respectively). Twenty-nine Mbale cases (41%) and ten Kapchorwa cases (33%) had a cough. Rigors and chills were noted in 70% (n=21) of cases at Kapchorwa compared to only 17% (n=12) of those at Mbale ($P < 0.001$).

Although the proportions of cases at both centres that could not localise painful stimuli did not differ, there was a difference in the proportions with low scores on the GCS but not the BCS. A greater proportion of those managed at Mbale, 48% (n=13), scored 3-8 on the GCS compared to only 25% (n=6) at Kapchorwa whereas 50% (n=3) of Kapchorwa cases scored 2 or less on the BCS compared to 63% (n=27) in Mbale. Anaemia (56%, $P = 0.05$) and jaundice (19%, $P = 0.06$) were more common in Mbale. The mean pulse rate was higher in Mbale (113 beats/min [95% CI 106-120]) than in Kapchorwa (110 beats per min [95% CI 100-119]) although this difference was not significant. Likewise the mean respiratory rate was higher in Mbale than Kapchorwa. A low pulse pressure (20-39 mmHg) occurred in 27% of Kapchorwa cases and 9% of Mbale cases. Most cases from Mbale, many of whom were children (41 cases aged 1-4 years and 13 cases aged 5-9 years), did not have measurements for blood pressure resulting in 57 cases (81%) with missing information on pulse pressure. Blood pressure cuffs that were not appropriate for very young children had been mistakenly ordered and it was impossible to get the right-sized ones despite several attempts. Shock and respiratory distress did not vary much between centres. However, 37 cases (53%) were noted to have one respiratory abnormality or the other in Mbale and only 5 cases (17%) in Kapchorwa ($P = 0.001$). There was a notable difference in the spleen size, with more cases in Mbale, 16 cases (23%), having enlarged spleens compared to Kapchorwa, 2 cases (7%).

Comparing the numbers of witnessed seizures showed no significant differences whether the number of witnessed seizures were categorised or left as continuous data. The proportion of survivors who were followed-up was 80% (n=24) in Kapchorwa and only 40% (n=28) in Mbale. None of the patients in Kapchorwa received loading doses of quinine on Day 0 whereas five cases in Mbale did (P value was not statistically significant). The proportion of early-onset sequelae (i.e. at time of discharge) did not vary between centres.

Changes in musculo-skeletal tone and reflexes were not different in patients at both centres. 5 Mbale cases (7%) and 5 Kapchorwa cases (17%) had complained of neck stiffness. 77% of cases (n=23) at Kapchorwa in unrousable coma at Level 2 compared to 74% of cases (n=52) at Mbale. Thirty-six Mbale cases had seizures (median = 2 [95% CI 2-3]) and ten Kapchorwa cases (median = 1 [95% CI 1-4]). On average Mbale cases took longer to clear their fevers, median of 3 days (95% CI 2-3), compared to 2 days (95% CI 1-3) in Kapchorwa, a difference which did not persist when the number of days reported with a fever before admission were added. The mean haemoglobin concentrations and parasite counts varied little between both groups. The mean Hb concentration was higher in Mbale than Kapchorwa (9.4 g/dL compared to 9.2 g/dL) but the mean parasite count in Mbale was lower than in Kapchorwa (12,683 parasites/μL compared to 26,215 parasites/μL). However both differences did not reach statistical significance. The random blood glucose was much higher in Mbale with a mean of 6.2 mmol/L than Kapchorwa where the mean was 4.9 mmol/L (P = 0.03).

4.8 Characteristics of cases by age group.

The major objectives of the study were to examine some of the age-related differences in the presentation and complications of cerebral malaria. *A priori* it was decided to use age as two categories, those between 1 year and 10 years (referred to as children), and those aged 10 years and above (referred to as 'adults' since after this age they should have clinical immunity to severe forms of malaria). An alternative was to group age on admission into three categories, namely 1 to 4 years (referred to as younger children), 5 to 9 years (referred to as older children), and 10 years and above. This second grouping of age was used when it was necessary to understand better what was happening within the 'children' category. Descriptive comparisons between children and adults were performed to identify any differences and elucidate factors that could influence the associations between age and outcomes. The results of comparisons are tabulated in Table 4.8.

Seventy-two cases were children and twenty-eight adults at the time of admission. The majority of those aged less than 10 years were *definite* cases whereas those in the older age group were equally distributed i.e. 50% *definite* and 50% *probable*. The male to female ratio amongst the younger group was 1:1 and in the older group it was 2.1:1. A greater proportion of adult cases survived (89%, n=25) compared to children (79%, n=57). The case fatality rate was 11% (n=8) in the children and 7% (n=2) in adults. Seven children were taken away from hospital prematurely. This contrasts with only one adult case. A greater proportion of children, 75% (n=54) were managed at Mbale hospital compared to 57% (n=16) of the adults. Only 25% (n=18) of the younger cases were managed at Kapchorwa and a greater proportion, 43% (n=12) of the older cases.

Table 4.8: Characteristics of cases by age group (N=100 cases)

Characteristics		< 10 years (n=72)		≥ 10 years (n=28)		P-value‡‡‡
		n	Percentage	n	Percentage	
CATEGORICAL DATA						
Demographic & History						
Case definition	Definite	44	*61*	14	*50*	0.37
	Probable	28	*39*	14	*50*	
Gender	Male	36	*50*	19	*68*	0.12
	Female	36	*50*	9	*32*	
Outcome	Survived	57	*79*	25	*89*	0.57
	Died	8	*11*	2	*7*	
	Taken away	7	*10*	1	*4*	
Centre	Mbale	54	*75*	16	*57*	0.09
	Kapchorwa	18	*25*	12	43	
Seizures with 24 hours before admission						
	None	15	21	9	32	0.11
	1-3	29	40	14	50	
	4-20	28	39	5	18	
Quinine given before admission		26	36	12	43	0.64
Previous medical admission		11	15	3	11	0.75
Clinical examination on admission						
Symptoms at Level 1						
	Fever	60	*83*	27	*96*	0.10
	Unconsciousness	49	*68*	17	*61*	0.49
	Confusion/Unawareness	34	*47*	22	*79*	**0.01**
	Convulsions	55	*76*	20	*71*	0.61
	Headache	31	*43*	24	*86*	**<0.001**
	Vomiting	28	*39*	14	*50*	0.37
	Loss of appetite	35	*49*	21	*75*	**0.02**
	Diarrhoea	9	*13*	3	*11*	1.00
	Cough	34	*47*	5	*18*	**0.01**
	Rigors and chills	18	*25*	15	*54*	**0.01**
Signs at Level 2						
Unable to localise painful stimuli		58	*81*	17	*61*	0.07
Blantyre coma score on admission (aged ≤5yrs)						
	0-2	30	*61*	-	-	-
	3-5	10	*21*	-	-	
	Not scored with BCS	9	*9*	-	-	
Glasgow Coma score (aged >5yrs)						
	3-8	11	*48*	8	*29*	**0.03**
	9-12	8	*35*	14	*50*	
	13-15	0	*0*	5	*18*	
	Not scored on GCS	4	*17*	1	*3*	
Moderate-severe anaemia		41	*57*	8	*29*	**0.01**
Jaundice		13	*18*	1	*4*	0.10
Moderate-severe dehydration		5	*7*	3	*11*	0.68
Pulse pressure	20-39	6	*8*	8	*29*	**<0.001**
	40-79	4	*6*	13	*46*	
	Missing info	62	*86*	7	*25*	
Shock		3	*4*	2	*7*	0.61

Table continued overleaf

‡‡‡ From Fischer's exact test

Table 4.8 continued

Characteristics	n	< 10 years (n=72) Percentage	n	≥ 10 years (n=28) Percentage	P-value§§§
Respiratory abnormality	39	*54*	3	*11*	**<0.001**
Respiratory distress	5	*7*	0	*0*	0.31
Extra heart sounds	11	*15*	2	*7*	**0.04**
Organomegaly	27	*38*	8	*29*	0.48
Enlarged spleen	16	*22*	2	*7*	0.09
Enlarged liver	17	*24*	3	*11*	0.17
Muscle tone changes (n=90)	40	*63*	11	*41*	0.06
Changes in tendon reflexes (n=86)	32	*51*	12	*44*	0.64
Neck stiffness	5	*7*	5	*18*	0.13
In-hospital non-laboratory information					
Seizures-1st episode					
None	38	*53*	16	*57*	0.39
1-3 seizures	21	*29*	10	*36*	
4-20 seizures	13	*18*	2	*7*	
Attended Follow-up	38	*53*	14	*50*	0.82
Quinine loading dose given on Day 0	6	*8*	1	*4*	0.78
Sequelae on discharge at Level 4 (n=90)	17	*24*	6	*21*	0.83
Not normally distributed		**Median (95% CI)**		**Median (95% CI)**	**P-value¶¶¶¶**
First dose of quinine given	32	*10 (10-11)*	12	*11(9-14)*	0.64
No. of witnessed seizures – 1st episode (n=46)	34	*3 (2-4)*	12	*1 (1-1)*	**0.005**
Seizure stoppage time (n=44 survivors)	32	*2 (1-2)*	12	*1 (1-3)*	0.48
Total seizure stoppage time (n=70 survivors)	49	*2 (2-3)*	21	*2 (1-4)*	0.66
Fever clearance time (n=78 survivors)	55	*3 (2-3)*	23	*2 (1-3)*	**0.03**
Total fever clearance time (82 survivors)	57	*5 (4-6)*	25	*5 (4-6)*	0.87
Coma recovery time (n=67 survivors)	45	*3 (2-4)*	22	*3 (3-4)*	0.54
Total coma recovery time (n=78 survivors)	54	*4 (3-4)*	24	*4 (3-5)*	0.31
Measurements taken on admission		**Mean (95% CI)**		**Mean (95% CI)**	**P-value††††**
Temperature (°C)	72	38.2 (38-38.4)	28	38 (37-38.5)	0.45
Respiratory rate (breaths/minute)	72	43 (40-46)	28	27 (24-29)	<0.001
Pulse rate (beats/minute)	72	116 (110-123)	28	101 (90-111)	0.01
Systolic blood pressure (mmHg, n=31)	10	107 (97-117)	21	105 (100-111)	0.79
Diastolic blood pressure (mmHg, n=31)	10	66 (57-75)	21	64 (59-68)	0.53
Haemoglobin concentration (g/dL, n=68)	48	9.0 (8.3-9.6)	20	10.3 (9.6-11.0)	**0.02**
Parasite count (parasites/µL, n=85) Geometric mean	61	16,936 (9,136-31,397)	24	13,764 (5,416-34,979)	0.61
Random blood glucose (mmol/L, n=70) Geometric mean	49	5.5 (4.7-6.4)	21	5.9 (5.2-6.7)	0.91
White blood cell count (cells/L, n=76) Geometric mean	53	6,583 (5,813-7,456)	23	4,970 (4,231-5,838)	**0.01**

§§§ From Fisher's exact test
¶¶¶ From Mann Whitney test
†††† From Student t-test except if the geometric mean was calculated in which case the Mann Whitney test was used

Of the ten symptoms asked for at Level 1, confusion (79%, n=22), headache (86%, n=24), loss of appetite (75%, n=21), and rigors and chills (54%, n=15) were more frequently reported by relatives of cases in the older group. Cough (47%, n=34) was more frequently reported in the younger group. Fever, unconsciousness, convulsions, vomiting, and diarrhoea did not differ between groups. Of those who could not localise painful stimuli the greater proportion were in the younger age group 81%, compared to 61% in the older group (P = 0.07). Most of those in the younger age group were scored using the BCS and the GCS was used for the older children over 5 years. Moderate to severe anaemia was more common in the under tens (57%) compared to those ten years and above (29%). When the age grouping with three categories was used, it showed that anaemia (determined by clinical examination or laboratory tests) was more frequent in those aged between 1 and 4 years (66%), than in those aged 5 to 9 years (18%) and those aged 10 years and above (16%). This was reflected in the value of the mean haemoglobin concentration which was significantly higher in the older group, 10.3 g/dL [95% CI 9.6-11], compared to the younger one, 8.9 g/dL [95% CI 8.2-9.6]. Jaundice did not however show this distribution, nor did dehydration.

The vital signs measured showed some differences between groups. Mean temperature did not differ (38.2 °C versus 38 °C), however in children, the mean respiratory rate, 44 breaths/minute (95% CI 41-47), and pulse rate, 117 beats/minute (95% CI 110-124) were higher than in adults, 27 breaths/min (95% CI 24-30) and 102 beats/min (95% CI 91-112) respectively, differences that are physiological. Many cases had missing values for blood pressure but of those measured both age groups had similar mean systolic and diastolic pressures. A greater proportion of cases in the older age group had lower pulse pressures. Respiratory abnormalities and extra heart sounds were more frequently found in children. Thirty-nine cases (54%) below 10 years had respiratory abnormalities and eleven cases (15%) had extra heart sounds detected. Respiratory distress was not found in any of the older children whereas shock was as frequent in both age groups. Twenty-two percent (n=16) of children had an enlarged spleen compared to two adult cases (7%).

Changes in musculo-skeletal tone were more frequently noted in younger (63%) cases than older ones (41%). However the same was not true of changes in their tendon reflexes which were noted fairly equally. Five cases (7%) in the younger group and five (18%) in the older group had neck stiffness on admission. Eight-one percent (n=58) of cases aged less than ten were in unrousable coma on admission compared to sixty-one percent (n=17) of cases aged ten and above. Younger cases had on average 3 seizures (95% CI 2-4) compared to older cases who on average had 1 seizure. Follow-up was attended by 38 cases, i.e. 53% of the younger group, and 14 cases, i.e. 50% of the older group. Around time of discharge, 24% of those less than 10 and 21% of those in the other group still had one neurological deficit or the other.

Children took on average 3 days to clear their fevers, a longer clearance time than the adult cases who took on average 1 and a half days (P = 0.02). The total fever clearance time however was 5 days in both age groups. The coma recovery time and seizure stoppage time were not very different between both groups. Likewise the mean parasite count and random blood glucose did not differ between groups. Younger cases had a larger mean white blood cell count than older cases (P = 0.01).

4.9 Summary of the differences of the characteristics of cases between case definition, study centre and age group.

The comparisons made thus far show much similarity of cases when categorised according to case definition, centre and age group. Some factors however were different between groups and as a result can modify the degree of associations between case definition, or study centre or age on the outcomes. Table 4.9 summarises the factors that differed within any group and gives the findings of comparisons in the other groups as well. These differences are taken into account in the analytical analyses in the next chapter.

Table 4.9: Statistical significance of effects of age group, centre, and differences between definite and probable cases.

Variable	Difference of comparison group		
	Case definition	Centre	Age group
Age on admission	0	++	NA
Gender	0	0	+
Outcome	++	0	0
Study centre	0	NA	+
Seizures prior to admission	+	++	+
Previous medical admission	0	+	0
History of			
Fever	0	0	+
Unconsciousness	0	+	0
Confusion/Unawareness	+	++	++
Headache	0	++	++
Convulsions	+	0	0
Vomiting	+	0	0
Loss of appetite	0	++	++
Cough	0	0	++
Rigors and chills	0	++	++
Unable to localise painful stimuli	++	0	+
Depth of coma among cases aged			
5 years and below	++	0	NA
Over 5 years	++	++	++
Presence of moderate to severe anemia	0	0	++
Presence of jaundice	0	0	+
Pulse pressure	+	++	++
Presence of any respiratory abnormality	0	++	++
Presence of any extra heart sounds	0	0	++
Presence of organomegaly (enlarged spleen and liver)	+	0	0
Presence of enlarged spleen	0	+	+
Presence of muscle tone changes	0	0	+
Presence of neck stiffness	0	0	+
Attended follow-up	0	++	0
Quinine loading dose given on Day 0	+	+	0
Median number of witnessed seizures – first episode	++	0	++
Median fever clearance time	0	++	++
Mean body temperature	++	0	0
Mean respiratory rate	++	+	++
Mean pulse rate	++	0	++
Mean haemoglobin concentration	0	0	++
Mean random blood glucose concentration	0	++	0
Mean white blood cell count	++	0	++

Key

++ = statistically significant difference with $p \leq 0.05$

\+ = borderline difference with $p > 0.05 \leq 0.1$

0 = no difference with $p > 0.1$

NA = not applicable

4.10 Description of the three study outcomes

The three neurological outcomes of interest namely mortality, early-onset sequelae and late-onset sequelae are described in detail in the following subsections

4.10.1 Mortality

Eighty-two cases are known to have survived and were discharged. Ten definitely died and eight cases were taken away from the ward by relatives before the completion of treatment. However one such case is known to have survived because the patient later returned to the hospital for follow-up. The pie chart in Figure 4.6 illustrates the frequency of the outcome of management

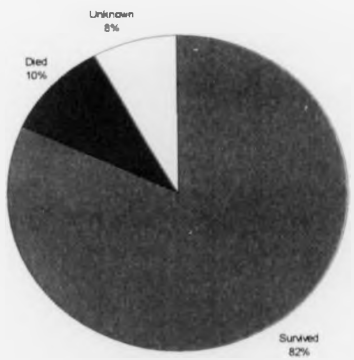


Figure 4.6: Pie chart illustrating the proportion of cerebral malaria cases who survived, died or whose outcome of management was unknown.

The overall case fatality rate was 10% (if the 7 cases with unknown outcome are removed from the denominator the CFR is 11%). Post-mortems were not performed on cases that died because there were no facilities to do so. It was therefore not possible to determine the causes of death.

Two cases died within a few hours of admission to the ward (case 1026 aged 10 years and case 1050, aged 2½ years). Since they did not spend a day their duration of stay was coded as 0.3. Table 4.10 below shows the survivor functions by length of stay up to 8 days. As can be seen, the predicted probability of survival decreases from 1 to 0.98 on Day 0 to 0.92 on Day 2. It remains constant thereafter to Day 48 which was the longest duration of stay.

Table 4.10: Duration of stay and the survivor function of study cases up to Day 8

Duration of stay (days)	Number of cases in study	Died	Lost	Survivor function	Standard Error
0.3‡‡‡‡	100	2	0	0.98	0.01
1	98	5	1	0.93	0.03
2	92	3	0	0.90	0.03
3	89	0	4	0.90	0.03
4	85	0	4	0.90	0.03
5	81	0	17	0.90	0.03
6	64	0	18	0.90	0.03
7	46	0	21	0.90	0.03
8	25	0	11	0.90	0.03

Figure 4.7 provides a further illustration of the predicted probability of survival in the form of a Kaplan-Meier graph. Each orange tick on the horizontal part of the step represents the number of censored patients on that day. Analysis time is the duration of inpatient stay for individual patients and is not constant. The longest duration of analysis time was 48 days but is not shown in the Figure. After Day 2, the survival function did not change. It is therefore plausible that those cases that were prematurely taken away by relatives stood a greater chance of surviving since all except one case, spent the first crucial 72 hours as inpatients (range 1-12 days). The one case (case number 1043) who was lost on Day 1, was 4 years old, was classified as a *probable* case (scored 3 on the BCS on admission), and was showing some signs of improvement before being taken away. As a result of these observations, mortality was considered within the first 72 hours as this was the maximum period during which mortality occurred and deaths could be verified. Even though there was no way of verifying the outcome of treatment in the eight cases who were prematurely taken away, it was assumed that since they spent the most crucial period of treatment on the ward and that they had began treatment, they were likely to have survived that episode of illness. And so, in subsequent analyses,

‡‡‡‡ Only used as a code and has no statistical importance

mortality refers to deaths within 72 hours on the ward and cases taken away prematurely were considered most likely to have survived

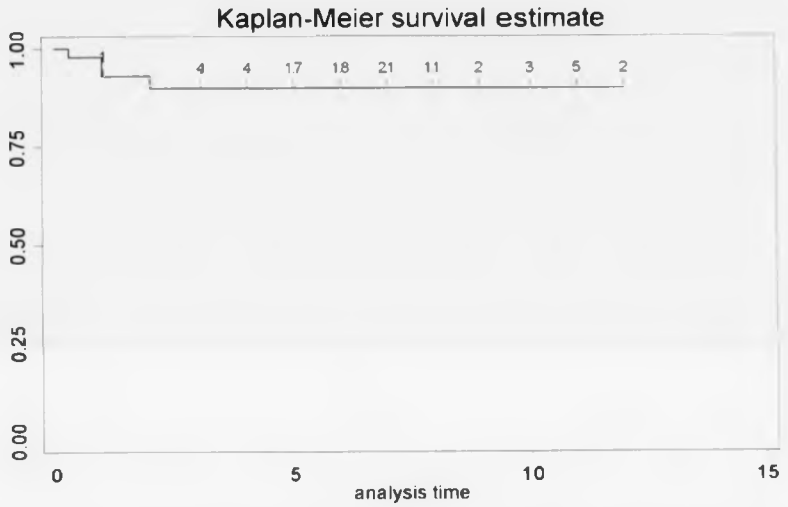


Figure 4.7: The estimated probability of survival (as Kaplan-Meier survival estimate) on Day 0 of treatment until Day 15

The estimated probability of survival by study centre (Figure 4 8) and age group (Figures 4 9) are illustrated in the graphs Each tick mark on the horizontal part of the steps represents a censored patient The numbers could not be represented clearly without congesting the graph Figure 4 8 shows the survival curves for both hospitals and those for the three age groups in Figure 4 9

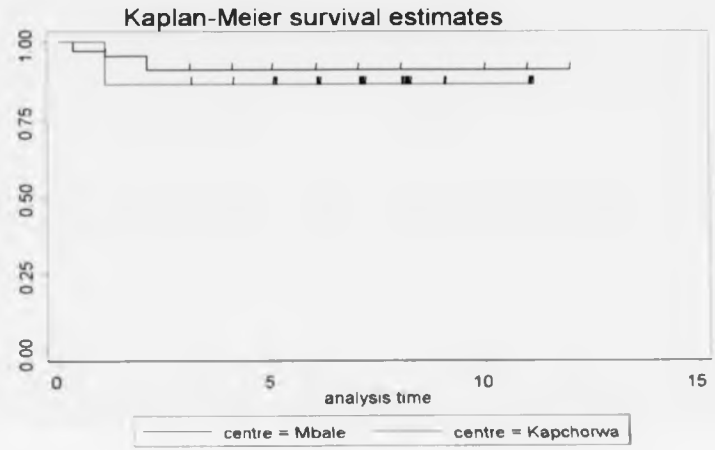


Figure 4.8: The estimated probability of survival (as Kaplan-Meier survival estimate) in 100 cases of cerebral malaria admitted to Mbale and Kapchorwa hospitals beginning on Day 0 of treatment until Day 15

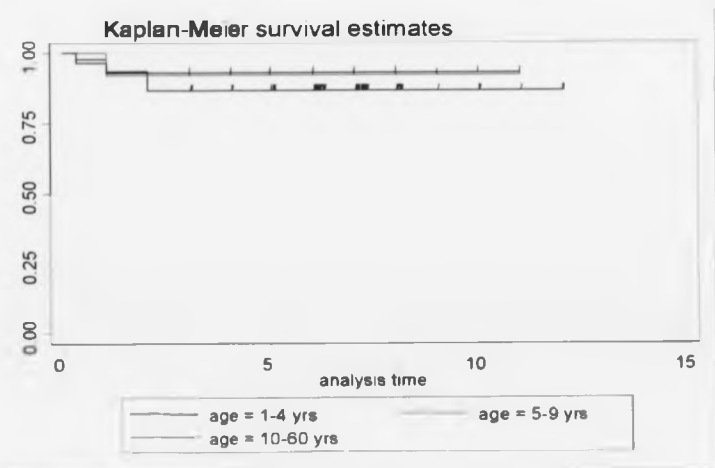


Figure 4.9: The estimated probability of survival (as Kaplan-Meier survival estimate) in 100 cases of cerebral malaria aged 1 to 4 years, 5 to 9 years, and 10 years and above, on Day 0 of treatment until Day 15

4.10.2 Early-onset neurological sequelae

Survivors were examined for neurological deficits of the motor-sensory kind at discharge. Twenty-three cases were found to have deficits (17 from Mbale and 6 from Kapchorwa hospitals). They had a median age of 72 months (95% CI 41-105) and a median between admission and detection of sequelae was 8 days (95% CI 6-9). Deficits occurred either singly (3 cases, 13%) or in combinations (20 cases, 87%) as shown in Table 4.11. The most common type of early-onset deficit was an abnormality of tone in the limbs (18 cases). Case number 2040 (a 6 years old child who spent 11 days on the ward) had seven types of deficits, the highest number recorded in combination. Case number 1055 (a 6 year old child who spent 48 days on the ward) had the next frequent number of deficits in one patient. By tying the deficits to form clinical pictures, the following neurological entities can be described (ranked in order of frequency):

- Generalised flaccidity of the limbs (cases 1067, 1340, 1118. 2040, 2090)
- Generalised spasticity of limbs (cases 1022, 1055, 1127)
- Paraparesis (cases 1126, 1137)
- Generalised hypotonia (case 1135, 1340)
- Weakness of upper limbs (case 2008)
- Hyperreflexia in one limb (cases 2019)
- Hypertonia in one limb (case 1108)
- Spastic hemiparaesis (case 1138)
- Hypertonia of the upper limbs (case 1105)
- Hypotonia of the lower limbs (case 2029)
- Monoparaesis in upper limb (case 1143)
- Monoparaesis in lower limb (case 2012)
- Cerebellar ataxia (case 1142)

Table 4.11: List of the twenty-three cases who had neurological deficits at discharge showing the types of deficits present.

Case Identification Number*****	Type of neurological deficit at discharge****												
	Tone abnormalities	Abnormal tendon reflexes	Reduced strength of limbs	Improper coordination of limbs	Cannot sit upright unsupported	Abnormal gait	Restricted eye movements	7th cranial nerve deficit	8th cranial nerve deficit	11th cranial nerve deficit	Visual impairment	Improper vocalisation	TOTAL
Aged 1-4 years on admission													
1022	X	X			X				X		X		5
1108	X	X	X		X	X							5
1129				X	X								2
1135	X	X		X									3
1137	X		X			X							3
1138	X	X	X			X		X					5
1142						X							1
1340	X	X	X		X	X							5
Aged 5-9 years on admission													
1055	X	X		X	X	X					X		6
1105	X											X	2
1106											X		1
1118	X	X	X		X	X							5
1126	X	X	X										3
2008	X	X	X										3
2012	X	X	X	X		X							5
2029	X	X											2
2040	X	X	X	X		X	X			X			7
Aged ≥ 10 years on admission													
1067	X		X		X								3
1079								X					1
1127	X	X		X		X							4
1143	X	X	X										3
2019				X		X							2
2090	X		X	X	X	X							5
TOTAL	18	14	12	8	8	12	1	2	1	1	3	1	

**** X signifies that the deficit was identified. A blank space means that the deficit was either absent or in a few cases that the deficit was not sought.

***** ID numbers beginning with '1' are from Mbale hospital while those beginning with '2' are from Kapchorwa hospital

Abnormalities of gait were observed in 12 patients. The patient with cerebellar ataxia (who was 4 years and spent 5 days) had an ataxic gait whereas two patients cases 1108 (2 years old and spent 7 days) and 1340 (16 months old and spent 10 days) were not able to walk at all. Case 2012 who was 8 years old (spent 11 days), had a weak right leg and had a limping gait. The eight other cases with gait abnormalities were able to walk but showed signs of weakness of their lower limbs. Two cases were not able to follow an object shown in front of them (a sign of visual impairment) but were not blind (cases 1055 and 1106, the latter was 6 years old and was on the ward for 5 days). Only one case, case number 1022, was blind at discharge. Case 1022 (16 months old and stayed 7 days), also appeared to have problems with hearing (the 8^{th} cranial nerve tested with the distraction test). Cases 1079 aged 16 years old (no recorded information on duration of stay), and 1138 aged 3 years old (stayed 8 days), had facial nerve palsies (7^{th} cranial nerve) on the left and right sides respectively. Both palsies were of the upper motor neurone type. Case 2040 had weakness on the left side when asked to turn the head or shrug the shoulders against resistance, i.e. a deficit of the 11^{th} cranial nerve.

In analytical analyses, the types of deficits or the severity of deficits could not be taken into consideration because of the small sample size and the few number of cases with early-onset sequelae.

4.10.3 Late-onset neurological sequelae

Follow-up visits were conducted at the study hospitals by the Principal Investigator at Kapchorwa hospital and the senior consultant paediatrician at Mbale hospital. During each visit a full clinical and neurological examination was conducted under the conditions specified in the methodology. Although the target was to assess for sequelae at 4 weeks, 8 weeks and 12 weeks after discharge, the duration between discharge and follow-up visits varied greatly. The median duration between discharge and the first visit in the 53 cases that attended was 4.7 weeks (range 2 days to 31.3 weeks) whereas the median duration between discharge and the second visit in 37 cases who returned was 9.4 weeks (range 5 to 39.4 weeks). This meant that the median duration between the first and second visits was 5 weeks (range 2.4 to 25 weeks). Six cases were assessed a third time and the median duration between discharge and visit was 19 weeks (range 14 to 36.4 weeks). The durations were

examined to determine if they were associated with the study centre, age grouping and case definitions. The median duration between the first visit was not associated with study centre (P = 0.9), age in two categories (P = 0.3), age in three categories (P = 0.6), and case definition (P = 0.7). The median duration between the second visit was not associated with age as two categories (P = 0.1), age as three categories (P = 0.2) and case definition (P = 0.2) but had some association with study centre, (P = 0.07). The median was 9 weeks in Mbale (n=18) and 15 weeks in Kapchorwa (n=19).

Table 4.12 below summarises the findings of the examinations of 10 cases that had neurological features suggestive of sequelae (i.e. 19% of cases that attended the first visit or 11% who survived). Five cases seen at Mbale hospital (17% of those who attended first visit; or 8% of those who survived) and five cases seen at Kapchorwa (21% of those who attended first visit; or 19% of those who survived) during follow-up were noted to have one kind of deficit or the other. The median age of the ten cases with late-onset deficits was 7½ years (range 1½ to 13 years). As described in the table the features of the sequelae varied in severity, character and timing.

Case 1029 (classified as a *definite* case), had mild weakness in all limbs that was not incapacitating. By the second visit, six weeks later, no deficits were detectable by clinical examination. The examining doctor did not detect any deficits in Case 1040 (a *probable* case) on the first visit. Five weeks later, the subject had developed repeated generalised seizures. Incapacitating sequelae were detected in Case 1055 (a *definite* case). These deficits had developed during the episode of cerebral malaria and by the first and second visits (2 and 7 weeks later respectively) there was no improvement. Case 1138 (a *definite* case) also had incapacitating complications which developed with cerebral malaria and had not recovered five weeks after discharge. Case 1143 (a *definite* case) had one episode of noctambulation that had not occurred before.

Table 4.12: A description of the findings of the neurological assessments of ten cases who had 'late-onset' neurological sequelae and the duration between their discharge date and follow up visit.

Case Number	Age*	Duration between discharge and visit (weeks)		Findings
		1st	2nd	
Aged 1-4 years on admission				
1040	1 year 6 months	6		1st visit on 17/4/02. Complaints of cough noted.
			11	2nd visit on 15/5/02. Complaints of an eye discharge and 3 convulsions noted. Description matched that for generalised convulsions.
1138	3 years 5 months	1		1st visit on 25/9/02. Not able to speak. Had right-sided hemiplegia. Power reportedly recovering from immediate post-admission levels. Right eye was deviated to the left and had right-sided facial nerve palsy.
			5	2nd visit on 23/10/02. Still not able to speak. Had right-sided weakness of the limbs. Still had leftward deviation of right eye and facial nerve palsy.
Aged 5-9 years on admission				
1055	6 years 4 months	2		1st visit on 3/7/02. Reportedly less attentive than prior to illness. Was having on average one convulsion per week since discharge. Description matched that of generalised convulsions. Reportedly not able to speak and hear as well as before. Could not walk and was not able to perform the finger-nose test. Neurological examination could not be conducted properly because the subject was inattentive and not cooperative.
			7	2nd visit on 7/8/02. Was still having convulsions although their frequency had reduced. Not able to talk and reportedly did not hear properly. Had rotatory nystagmus. Was not able to carry instructions for the neurological examination.
1029	7 years	5		1st visit on 17/4/02. Reduced power detectable in all limbs but more in left arm.
			11	2nd visit on 29/5/02. Power noted to be normal in all limbs.
2040	7 years	1		1st visit on 16/1/03. Reported not to be able to stand upright and not able to dress up without help. Had headaches on and off and got tired easily. Had left-sided hemiplegic gait. Had a right-sided squint (which developed on the 3rd day as an inpatient) and left-sided facial nerve palsy. Had left-sided hemiparaesis. A pan-systolic murmur was detectable†.
			8	2nd visit on 6/3/03. No squint visible. Strength in the left leg had improved and was equal to the right leg. Complained of left-sided chest pain. Had a pan-systolic murmur. Chest X-ray showed an enlarged heart.

Table continued overleaf

* Age on the first follow-up visit
† Child with a cardiac lesion

Table 4.12 continued

Case Number	Age‡	Duration between discharge and visit (weeks)		Findings
		1st	2nd	
2011	7 years 4 months	29		1st visit on 28/11/02. Reportedly had general weakness that had not improved since illness. Experienced one restless night. Power was noted to be normal.
			36	2nd visit on 16/1/03. Reportedly had more strength but still weaker than state before bout of cerebral malaria. Power was noted to be normal in all limbs.
Aged ≥ 10 years on admission				
1143	11 years 6 months	4		1st visit on 6/11/02. Complaints of cough. Had dizziness after recovering from cerebral malaria which improved over time and is no longer there.
			9	2nd visit on 11/12/02. Had began to wake up at night and walk about (i.e. sleep walk)
2020	12 years	21		1st visit on 30/11/02. Reportedly not able to remember events/people/things as well as prior to illness. Was less attentive when spoken too and did not carry out instructions given as well as prior to illness. Had headaches on and off.
			28	2nd visit on 17/1/03. No improvement in memory or ability to follow instructions. No longer had headaches.
2090	12 years	4		1st visit on 6/2/03. Reported not able to remember events/people/things as well as prior to illness of cerebral malaria. Had headaches on and off. Also noted to be less attentive when spoken to. Walked with a stagger and was abnormal for the heel-to-toe test. But no other signs of cerebellar ataxia
			19	2nd visit on 16/5/03. Reported less forgetful although memory had not completed recovered to pre-illness capacity. Headaches were reducing in frequency and intensity. Was walking normally and was able to do the heel-to-toe test properly.
2025	14 years 7 months	23		1st visit on 28/11/02. Reportedly not able to remember events/people/things as well as prior to illness. Was more emotionally labile than before. Had headaches on and off.
			30	2nd visit on 16/1/03. Was less forgetful. Headaches had reduced in frequency and intensity.

‡ Age on the first follow-up visit

The cases examined at Kapchorwa showed a similar pattern to those seen at Mbale. Case 2011 (a *probable* case) reportedly had general body weakness suggestive of reduced muscle strength that had improved by the first visit (29 weeks later). There was a history of an episode of hallucinations at night but no other relevant complaint by the second visit (7 weeks after the first visit). Memory dysfunction was reported in Case 2020 (a *definite* case) by the first visit (21 weeks later). Loss of concentration, a cognitive function, was also a complaint. Both functions had not improved by the second visit, 7 weeks later. On the first review, Case 2025 (a *probable* case) had reported memory impairment with a tendency to become very emotional. Thirty weeks after discharge there was improvement in memory and was having fewer headaches. Case 2040 (a *definite* case) had incapacitating complications that began during disease and were still present at the first and second visits, although some improvement in muscle strength had occurred by the second visit. The subject had a concomitant cardiac lesion. Case 2090 (a *probable* case) reportedly had memory and concentration loss since illness. The subject had weakness of the lower limbs which had recovered by the second visit. Memory function has also improved but not fully recovered.

Some cases with detectable late-onset deficits were detected to have early-onset deficits as well suggesting that the term 'late-onset' sequelae as defined *a priori* is inappropriate. Four cases who had deficits by the first visit also had deficits on discharge (cases 1055, 1138, 2040, and 2090) and one case who had early deficits did not have deficits at the first visit (case 1143). By the second visit the one case who had early deficits but none at the first visit (case 1143) developed late deficits. Four cases who did not have detectable deficits at discharge went on to develop deficits by the first visit (cases 1029, 2011, 2020, and 2025). One case, who did not have deficits at discharge and at the first visit had developed deficits by the second visit (case 1040). Clinical examination at discharge detected early-onset deficits and was 50% sensitive enough to identify cases that had deficits at the first visit (specificity of 50%, positive predictive value of 80% and negative predictive value of 20%).

Audiometry was performed in 50 cases during follow-up on the first visit. One case (case 1055) was found to have hearing deficits in both ears. None of the cases (n=51) whose visual acuity was tested showed any visual impairment. Case 1022 who was blind on admission had improved by the first follow-up visit about 5 weeks later. Case 1055 who had visual impairment at discharge improved by the first visit about 2 weeks later. The other case with visual impairment, case 1106, did not attend follow-up. No case had any identifiable abnormalities on fundoscopy either during follow-up.

Thus far the 'late-onset' sequelae that have been described are mostly of the motor-sensory kind. The findings of cognitive assessment are given separately because their identification involved a separate process as documented in the methodology.

4.10.4 Cognitive sequelae determined with the cognitive tool for children

One version of the cognitive tool was used to assess children that attended follow up visits. Twenty-four children did the language and verbal comprehension sections (LGVC) and nineteen children did the memory sections (MEM). Their average scores on both visits are tabulated in Table 4.13.

Table 4.13: The median scores obtained during follow-up in children who were assessed for cognitive function

Instruction	Median (variance)	
	First visit	Second visit
LGVC1* (n=24)	6 (1.5)	6 (1.5)
LGVC2	6 (1.5)	6 (1.6)
LGVC3	6 (1.5)	6 (3.0)
LGVC4	6 (3.1)	6 (1.6)
LGVCtotal†	24 (25.0)	24 (25.8)
MEM1‡ (n=19)	5 (2.1)	5 (3.1)
MEM2	3 (1.3)	3 (0.6)
MEMtotal§	8 (5.5)	8 (5.1)

* Language and verbal comprehension instruction number 1 and so on.
† Sum of the four LGVC scores.
‡ Memory test instruction number 2 and so on
§ Sum of the two memory scores

The median scores did not vary between visits. Some of the individual instructions had narrow distributions (small variance) among the children whereas others such as language and verbal comprehension 3, language and verbal comprehension 4, and memory 1 had wider distributions (large variances). The totals, language and verbal comprehension total and memory total, also had wide distributions.

The cut-off scores described in the methodology were used to classify subjects into two groups, namely those who are likely to have cognitive dysfunction and those who are unlikely to have cognitive dysfunction. A summary of the findings are given in Table 4.14. Ten children (11% of survivors and 26% of children aged less than ten years that attended follow-up) were classified by the cognitive tool to have some cognitive dysfunction. The median age of the ten children was 6 years (range 3-8 years) and the ratio of males to females was 1:1. Six children attended Mbale hospital and four Kapchorwa hospital. Five cases identified with cognitive deficits were found to have motor-sensory deficits on discharge i.e. early-onset deficits. Four children identified with cognitive deficits also had motor-sensory deficits that were identified during follow-up i.e. late-onset deficits. Three survivors, cases 1055, 1138 and 2040 had motor-sensory deficits at discharge and during follow-up and were identified to have cognitive sequelae by the cognitive tool.

Table 4.14: Summary of the neurological sequelae identified by clinical examination and cognitive assessment (using the child version[**]) among survivors of cerebral malaria.

Case Number	Early-onset deficits identified[††]	Late-onset deficits identified[‡‡]		Cognitive deficits identified					
				MEMtotal		LGVC2		LGVCtotal	
		1st visit	2nd visit	1st visit	2nd visit	1st visit	2nd visit	1st visit	2nd visit
Child									
1021	No	No	No	**Yes**	No	No	No	No	No
1022	**Yes**	No	No	NA[§§]	NA	NA	NA	NA	NA
1029	No	**Yes**	No	No	No	No	No	No	No
1033	No	No	No	**Yes**	**Yes**	No	No	No	No
1040	No	No	**Yes**	NA	NA	NA	NA	NA	NA
1055	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
1105	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1106	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1108	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1117	No	No	No	No	No	No	**Yes**	No	No
1118	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1126	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1129	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1135	**Yes**	No	No	**Yes**	**Yes**	No	No	No	No
1137	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1138	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	No	No	**Yes**	**Yes**
1142	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1143	**Yes**	No	**Yes**	No	No	No	No	No	No
1340	**Yes**	No	No	NA	NA	NA	NA	NA	NA
2008	**Yes**	No	No	NA	NA	NA	No	NA	No
2011	No	**Yes**	No	No	**Yes**	No	No	No	No
2012	**Yes**	No	No	**Yes**	**Yes**	No	No	No	No
2029	**Yes**	No	No	NA	No	NA	No	NA	No
2040	**Yes**	**Yes**	**Yes**	**Yes**	No	No	No	No	No
2041	No	No	No	No	**Yes**	No	No	No	No
Adult									
1067	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1079	**Yes**	No	No	NA	NA	NA	NA	NA	NA
1127	**Yes**	No	No	NA	NA	NA	NA	NA	NA
2019	**Yes**	No	No	NA	NA	NA	NA	NA	NA
2020	No	**Yes**	**Yes**	NA	NA	NA	NA	NA	NA
2025	No	**Yes**	**Yes**	NA	NA	NA	NA	NA	NA
2090	**Yes**	**Yes**	**Yes**	NA	NA	NA	NA	NA	NA
Total positive	**23**	**8**	**8**	**7**	**7**	**1**	**2**	**2**	**2**

[**] Some adults have been included here that were not assessed with either version of the cognitive tool.

[††] Motor-sensory deficits were examined for at discharge

[‡‡] Motor-sensory deficits were examined for during follow-up and some cognitive deficits were reported by the relative who accompanied the subject for follow-up.

[§§] Not applicable because the instruction/test was not performed either because the subject did not come for the visit or the tool was not available for assessment.

4.10.5 Cognitive sequelae determined with the adult version of the cognitive tool

Ten adult subjects (all seen at Kapchorwa) were assessed using the adult version of the cognitive tool. Their results are summarised in Table 4.15. One subject did not score the maximum score on the orientation score because she was shy during the assessment. The two subjects who ranked highest on picture identification and recall, and digit recall did not have reported changes that suggested any cognitive dysfunction after the episode of cerebral malaria. The other subjects except case number 2022, who ranked below the first two did less well on the tests and also had reported behaviour changes suggestive of either memory impairment (6 subjects) or attention deficits (4 subjects). Case 2022 was shy during the assessment and did not score highly. Case 2013 was not assessed with the cognitive tool, As a result of these findings, six cases (cases 2020, 2021, 2025, 2087, 2089, 2090) were classified as having or having had some cognitive dysfunction after cerebral malaria (median age 12½ years, range 11-14). Three cases with cognitive sequelae had late-onset deficits (cases 2020, 2025 and 2090). Case 2090 had early-onset deficits as well.

Table 4.15: Summary of the findings of adult subjects who were assessed with the adult version of the cognitive tool and ranked in decreasing order of performance on their first visit.

Case number	Age on first visit (years)	Reported behaviour changes on 1st visit*	Orientation score†		Number of pictures correctly identified out of ten		Number of pictures correctly recalled out of ten		Number of digits correctly recalled out of six		Remarks
			1st visit	2nd visit	1st visit	2nd visit	1st visit	2nd visit	1st visit	2nd visit	
2017	13	No	5	5	10	10	9	8	3	2	No seizures reported
2018	13	No	5	5	10	9	9	8	3	4	No seizures reported
2025	15	Yes	5	5	10	10	6	9	2	0	No seizures reported; Reportedly was forgetful after illness and was more emotional than before illness.
2021	14	Yes	5	NA‡	9	NA	7	NA	3	NA	No seizures reported; Reportedly was forgetful after illness, was less attentive and sometimes not able to speak properly.
2090	12	Yes	3	4	9	7	7	5	1	6	No seizures reported; Was shy during 1st assessment. Reportedly was forgetful after illness and was not as attentive.
2022	13	No	5	NA	9	NA	5	NA	4	NA	No seizures reported; Was shy during assessment.
2087	13	Yes	5	5	8	10	7	10	3	6	No seizures reported; Reportedly was forgetful after illness and less attentive
2089	13	Yes	5	NA	8	NA	5	NA	4	NA	No seizures reported; Reportedly was forgetful after illness.
2020	12	Yes	5	5	8	6	5	4	3	0	No seizures reported; Was shy during both assessments. Reportedly was forgetful after illness and was not as attentive.
2013	13	No	5	5	NA	NA	NA	NA	NA	NA	No seizures reported; Cognitive tool was not used for assessment

* Five questions were asked about subjects' behaviour comparing memory, attention, and emotions before illness with cerebral malaria and the period after.
† Maximum score of five and minimum of zero
‡ Not applicable because the test was not performed.

Chapter 5

This chapter contains the analytical results of univariate, bivariate and multivariable analyses. Apart from presenting the findings, as I did in the previous chapter, I will on a few occasions relate the findings with each other in order to make the text easier to read.

5. ANALYTICAL RESULTS

The analyses focused on a) elucidating the association between age of onset of disease and outcomes, i.e. the study hypothesis, b) identifying independent risk factors for the outcomes c) and quantifying the magnitude of important measures of associations. Measures of association between explanatory factors and the outcomes are presented as relative risk estimates. As a result of the small sample size and the low frequency of outcomes, the ability of the study to estimate the strength and magnitude of associations is limited. Reference will be made to statistically and clinically significant relationships as well as important null results.

5.1 Risk factors for mortality

Relative risk estimates as crude odds ratios are presented first. Bivariate results in which the crude ORs are adjusted for hospital, or case definition or age are presented next. The findings of fitting logistic models to the data are given finally.

5.1.1 Relative risk estimates determined by univariate analysis

All one hundred cases were used to determine those factors which were associated with mortality within 72 hours of admission. Table A in Appendix V gives the number of deaths, survivors, and the odds for death for relevant explanatory variables. Table 5.1 below shows the odds ratios for death (derived from odds) for categories that contained events.

Table 5.1: Univariate odds ratios for mortality among cases admitted with cerebral malaria (N=100)

Variable	Coefficient	Standard error	P-value	Odds ratio	Lower 95% CI	Upper 95% CI
Demographic & History information						
Centre (Mbale/Kapchorwa)	0.4953	0.686	0.47	1.64	0.42	6.36
Age (less than 10 years/10 and above)	-0.4855	0.824	0.55	0.62	0.12	3.13
1-4 years				1		
5-9 years	-0.5878	0.856	0.49	0.55	0.10	3.02
10 and above	-0.6678	0.854	0.43	0.51	0.09	2.79
Seizures within 24 hours prior to admission						
None				1		
1-3 seizures	-1.6854	0.881	**0.05**	0.19	0.03	1.12
4-20 seizures	-0.9676	0.786	0.21	0.38	0.08	1.84
Quinine given prior to admission (No/Yes)	-1.8379	1.075	0.09	0.16	0.02	1.38
Previous medical admission to hospital (No/Yes)	-0.4183	1.095	0.70	0.66	0.08	5.71
Clinical examination on admission						
Able to localise painful stimuli at Level 1 (No/Yes)	-0.8472	0.721	0.24	0.43	0.10	1.80
Body temperature						
35.0-38.5 °C				1		
38.6-39.4 °C	-0.3137	0.850	0.71	0.73	0.14	3.91
39.5-42.0 °C	0.9985	0.909	0.27	2.71	0.44	16.61
Moderate – severe anaemia (No/Yes)	-0.4055	0.679	0.55	0.67	0.17	2.55
Clinical signs of moderate – severe dehydration (No/Yes)	0.2757	1.125	0.80	1.32	0.14	12.09
Presence of extra heart sounds (No/Yes)						
None				1		
Yes	0.3483	1.161	0.76	1.42	0.14	13.99
Missing info	2.1400	0.751	**0.004**	8.50	1.75	41.19
Pulse pressure						
20-39 mmHg	-0.2076	1.462	0.88	0.81	0.05	14.28
40-79 mmHg				1		
Missing info	0.5335	1.103	0.62	1.70	0.20	14.83
Respiratory abnormality (No/Yes)	-0.0918	0.679	0.89	0.91	0.23	3.48
In-hospital non-laboratory information						
First episode of witnessed seizures (none/any number)	-2.3250	1.070	**0.03**	0.10	0.012	0.80
None				1		
1-3 seizures	-1.9196	1.075	**0.04**	0.15	0.02	1.29
Quinine loading dose prescribed on admission						
No				1		
Yes	1.0986	1.196	0.35	3.00	0.28	32.15
Missing	0.9444	0.765	0.21	2.57	0.56	11.76
Total amount of quinine given on Day 0						
225 – 569 mg				1		
570 – 1800 mg	-0.7732	0.896	0.38	0.46	0.08	2.73
Missing info	0.8754	0.771	0.25	2.40	0.51	11.21

Table continued overleaf

Table 5.1 continued

Variable	Coefficient	Standard error	P-value	Odds ratio	Lower 95% CI	Upper 95% CI
Laboratory based information						
Random blood glucose on Day 0						
Less than 5 mmol/L	0.9163	1.261	0.46	2.50	0.21	29.60
5 – 6.9 mmol/L				1		
7 and above	0.1743	1.444	0.90	1.19	0.07	20.21
Missing info	1.8326	1.117	0.10	6.25	0.70	55.84
Parasite count on Day 0						
50,000 parasites/µL and below				1		
> 50,000 parasites/µL	1.4961	0.869	0.08	4.46	0.78	25.67
Missing info	1.8325	0.967	0.06	6.25	0.87	45.14
Haemoglobin concentration						
3.0-9.9 g/dL			0.58	1.65	0.28	9.83
10.0-15.0 g/dL				1		
Missing info	0.1941	0.751	0.44	2.00	0.33	12.09
Serum Sodium concentration						
<135 mmol/L			0.39	2.62	0.26	26.2
135-146 mmol/L	-0.9634	1.156		1		
>146 mmol/L	0.0351	1.194	0.49	2.71	0.14	53.62
Missing info	-0.1881	0.750	0.49	2.17	0.22	21.44
Serum Calcium concentration						
2-3 mmol/L				1		
Missing info	16.4435	0.753	0.67	0.62	0.07	5.84
Serum Chloride concentration						
95-105 mmol/L				1		
>105 mmol/L	15.5321	1.074	0.15	4.25	0.48	37.53
Missing info	16.3729	0.902	0.50	1.83	0.31	10.99

The case fatality rate was higher in Kapchorwa and as a consequence the risk of death as estimated by the odds ratio showed that those cases managed at Kapchorwa hospital had a 64% greater risk of death than those managed in Mbale (OR=1.64 [95% CI 0.42-6.36]). Adults were about 40% less likely to die than children. Those cases that did not have a history of seizures within 24 hours before admission were at greater risk of death compared to cases who reportedly had 1-3 seizures or 4-20 seizures. Cases that received quinine prior to admission were less likely to die than those who did not, OR 0.16 (95% CI 0.02-1.38). Of those who received quinine prior to admission (n=38), 10% did not report any seizures within 24 hours before admission, 53% reported 1-3 seizures and 37% reported more than 3 seizures (P = 0.04 from Fisher's exact test). However the median number of reported seizures among those who gave a history of quinine use and those who did not was not significantly different. On admission, cases who could not localise painful stimuli were just over 50% more likely to die than those who were in less deep coma. Having a temperature over 39.6°C was more likely to predispose to death (OR 2.71 [95% CI 0.44-16-61]) than having temperatures between 35-38.5 °C. There was little difference in risk of those with temperatures between 38.6-39.4 and the lower category.

The presence of moderate to severe anaemia appeared to be associated with a lower risk of death by 33% though the study did not have sufficient power to identify this association as a real one. The opposite occurred in those who had moderate to severe dehydration. Dehydrated cases had an odds ratio of 1.32 (95% CI 0.14-12.09) compared to those who were not found to be dehydrated. The detection of extra heart sounds was associated with a 42% increase in risk compared to those without extra heart sounds. Those who were not examined for extra heart sounds were at greater risk of death (OR 8.50 [95% CI 1.75-41.19]) than those who did not have extra sounds (auscultation was always done by a doctor). Similarly, those with missing information on pulse pressure had a greater odds ratio (OR 2.1 [95% CI 0.24-18.4]) when compared to those with a pulse pressure 40-79 mmHg. Those with pulse pressures in the lower range, 20-39 mmHg had a greater risk (OR 1.23 [95% CI 0.07-22.71]) than those in the middle category (blood pressure, pulse rates and respiratory rates were determined by a nurse).

When the occurrence of tonic-clonic seizures was compared with the absence of seizures, an OR of 0.10 (95% CI 0.02-1.29) was obtained, that is to say, death appeared less likely in those with seizures. The fever clearance times and parasite clearance times were not used in these analyses because these two features did not have sufficient time to resolve before death occurred. Giving a loading dose of quinine when compared against not giving a loading dose produced a risk estimate of 3 (95% CI 0.28-32.15). Those without recorded information about whether they received a loading dose of quinine had a risk estimate of 2.57 (95% CI 0.56-11.76) compared to those who did not receive a loading dose.

Using the reference concentration of 5-6.9 mmol/μL for random blood glucose, comparisons were made with other glucose concentrations. Those with less than 5 mmol/μL had a 2.5 fold (95% CI 0.02-30.83) greater risk of death, and those with concentrations over 7 mmol/μL had 1.2 fold (95% CI 0.07-20.83) greater risk of death. Those with no information on random blood glucose were at the highest risk of death with an OR of 6.25 (95% CI 0.64-61.00).

The higher parasite counts on Day 0 were associated with a greater risk of death. The risk increased by about 4 times when the count was over 50,000 parasites/μL. It was even higher if the count was not done (OR=6.25). Patients with HB concentrations in the lower category when compared with those with Hb 10-15 g/dL had an OR of 1.65 and those without information on Hb concentration had an OR of 2.0 when compared to the same group. Lower than normal serum sodium concentrations were associated with a higher risk of death (OR 2.62 [95% CI 0.26-26.2]) compared to those within the normal range. Those with higher concentrations or missing information were also at a higher risk (OR 2.71 [95% CI 0.14-53.62] and OR 2.17 [95% CI 0.22-21.44] respectively). In contrast, those with no information on serum calcium had a lower OR (0.62 [95% CI 0.07-5.84]) than those within the normal range. Cases with serum chloride above 105 mmol/L were 4 times at risk of death compared to those with a normal range of chloride. Cases that did not have their serum chloride concentration estimated were about 2 times more likely to die.

5.1.2 Adjusted relative risk estimates determined by bivariate analysis

The effect of case definition (N=58), study centre and age (N=100) on the risk factors for mortality were examined separately. The adjusted odds ratios resulting from these analyses are summarised in Table 5.2. A number of factors were excluded from these analyses because, either i) cases with the outcome did not accrue sufficient information on the factor, such as coma score, or ii) it was not considered relevant to include them, such as the kinds of symptoms. Factors that were shown to differ within each group (i.e. between centre, case definition and age group) in the descriptive analyses were examined first, since they had a greater potential to influence the associations between explanatory factors and mortality.

A number of associations were influenced by the hospital where the patient was managed. The relative risk slightly decreased among the older children when centre was controlled for. Patients who received a loading dose of quinine were twice as likely to die as those who did not although this was not statistically significant. This adjusted estimate of relative risk was less than the unadjusted one although the confidence interval was narrower. The adjusted risk when the parasite count was over 50,000 parasites/μL was about 4 times greater compared to 50,000 parasites/μL and below. This risk was even greater when the degree of parasitaemia was not assessed.

The relative risk estimates after adjusting for age are also presented in the same Table. Univariate estimates which were modified either in terms of the value of the estimate or reducing the width of the confidence intervals, are whether a loading dose of quinine was given prior to admission, random blood glucose concentration, absence of a history of seizures prior to admission, absence of seizures on the ward, higher degree of parasitaemia and greater time taken to clear the parasitaemia. Those who did not have a history of seizures were less likely to die than those who had a history of between 1 to 3 seizures.

Table 5.2: Adjusted Odds ratios for mortality.

Risk factor	Unadjusted OR	Variable adjusted for: Case definition OR	95% CI	Centre OR	95% CI	Age group OR	95% CI
Factors shown to have differences in the descriptive analyses							
Centre							
Mbale	1	1		NA	-	1	
Kapchorwa	1.64	2.00	*0.47-8.50*	-	-	1.80	*0.45-7.12*
Age group 1							
≤ 10 yrs	1	1		1		NA	-
> 10 years	0.62	0.75	*0.14-4.10*	0.55	*0.11-2.87*	-	-
Age group 2							
1-4 yrs	1	1		1		NA	-
5-9 yrs	0.55	0.76	*0.13-4.46*	0.24	*0.02-3.17*	-	-
10 yrs and above	0.51	0.69	*0.12-4.06*	0.44	*0.07-2.77*	-	-
Seizures within 24 hours before admission	0.27	0.14	*0.03-0.73*	0.27	*0.06-1.18*	0.25	*0.06-1.00*
Number of seizures within 24 hours prior to admission							
None	1	1		1		1	
1-3 seizures	0.19	0.11	*0.01-0.93*	0.20	*0.03-1.23*	0.19	*0.03-1.10*
4-20 seizures	0.38	0.17	*0.03-1.09*	0.39	*0.06-2.51*	0.29	*0.05-1.60*
Admitted to hospital before	0.66	0.65	*0.07-6.10*	0.75	*0.08-7.01*	0.63	*0.07-5.68*
Body temperature							
35.0-38.5 °C	1	1		1		1	
38.6-39.4 °C	0.73	0.44	*0.08-2.55*	0.70	*0.13-3.87*	0.77	*0.14-4.17*
39.5-42.0 °C	2.71	1.33	*0.21-8.57*	2.67	*0.42-16.97*	2.85	*0.48-16.93*
Presence of moderate to severe anaemia	0.67	0.48	*0.12-1.96*	0.72	*0.18-2.90*	0.61	*0.17-2.19*
Presence of any respiratory abnormality	0.91	0.67	*0.16-2.71*	1.10	*0.22-5.42*	0.79	*0.24-2.63*
Presence of any extra heart sounds							
No	1	1		1		1	
Yes	1.42	1.39	*0.13-14.74*	1.32	*0.13-13.93*	1.22	*0.18-8.05*
Missing info	8.50	24.38	*2.30-258.82*	8.19	*1.73-38.73*	5.77	*1.41-23.66*
Pulse pressure							
20-39 mmHg	1.23	0.83	*0.04-19.25*	1.20	*0.08-18.35*	1.05	*0.03-33.52*
40-79 mmHg	1	1		1		1	
Missing info	2.10	1.08	*0.11-10.80*	2.26	*0.39-13.21*	3.41	*0.14-79.53*
Had witnessed seizures	0.10	0.06	*0.00-0.61*	0.11	*0.01-1.08*	0.11	*0.01-0.99*
Had 1-3 witnessed seizures on first episode	0.15	0.08	*0.01-0.87*	0.17	*0.02-1.62*	0.17	*0.02-1.50*
Loading dose of quinine given on admission							
No	1	1		1		1	
Yes	3.00	1.30	*0.13-13.45*	2.08	*0.19-22.43*	1.75	*0.17-18.19*
Missing info	2.57	4.88	*0.80-29.74*	2.34	*0.48-11.51*	2.40	*0.54-10.72*

Table continued overleaf

Table 5.2 continued

Risk factor	Unadjusted OR	Variable adjusted for: Case definition OR	*95% CI*	Centre OR	*95% CI*	Age group OR	*95% CI*
Random blood glucose							
< 5 mmol/L	2.50	2.18	*0.17-27.56*	2.43	*0.20-28.91*	2.27	*0.18-28.54*
5-6.9 mmol/L	1	1		1		1	
≥7 mmol/L	1.19	0.92	*0.05-16.46*	1.33	*0.08-23.20*	1.11	*0.06-19.38*
Missing info	6.25	6.00	*0.62-57.68*	6.46	*0.72-58.11*	5.82	*0.63-53.93*
Haemoglobin concentration							
3.0-9.9 g/dL	1.65	1.27	*0.20-8.08*	1.69	*0.27-10.64*	1.77	*0.27-11.41*
10.0-15.0 g/dL	1	1		1		1	
Missing info	2.00	2.33	*0.34-15.90*	2.18	*0.35-13.58*	1.85	*0.27-12.46*
Other explanatory factors							
Quinine given prior to admission	0.16	0.16	*0.02-1.45*	0.15	*0.02-1.40*	0.16	*0.02-1.41*
Parasite count							
≤ 50,000 parasites/μL	1	1		1		1	
> 50,000 parasites/μL	4.46	5.54	*0.87-35.26*	4.08	*0.87-19.18*	4.32	*0.78-23.92*
Missing info	6.25	15.50	*1.31-183.14*	7.97	*0.91-70.14*	6.56	*0.83-51.66*

A parasite count over 50,000 parasites/μL was associated with a fourfold increase in risk of not surviving compared to a count less than that. When the count was not done the risk was six and a half times greater than if the count was in the lower category and about one and a half times (OR 1.28 [95% CI 0.29-6.62]) greater than if the count was in the higher category.

The effect of the case definition on the association between factors and survival was examined and the result shown in Table 5.2. The number of cases used for this analysis is 58 because *probable* cases did not contribute to this outcome. Even with this restriction the strength of the associations shown in the table were not significantly modified. Kapchorwa cases were twice as likely not to survive compared to Mbale cases, an increase from the unadjusted estimate. A history of seizures within 24 hours prior to admission was associated with a reduced OR of 0.14 (95% CI 0.03-0.73) when compared to those without such a history (P = 0.01). The OR remained smaller with increasing levels of seizure numbers.

Case definition modified the magnitude of the risk estimate between outcome and body temperature. Those with temperatures in the highest category were at greater risk of not surviving (OR 1.33 [95% CI 0.21-8.57]) which was less than the finding in univariate analysis (OR 2.71 [95% CI 0.44-16.61]). Those with temperatures between 38.6-39.4°C were about 50% less likely to die than those with temperatures between 35.0-38.5 °C which was similar to the unadjusted value. The presence of severe to moderate anaemia was less likely to be associated with risk for the outcome (OR 0.48) than its absence although this finding was not found to be statistically significant.

Having any number of seizures while on the ward resulted in a smaller relative risk even among the *definite* cases. This finding was unlikely to be accidental and the P value was low (P < 0.001). The relationship between the degree of parasitaemia and survival was examined among *definite* cases. The adjusted OR was 5.54 (95% CI 0.87-35.26) if those in the higher group were compared to those in the lower group; an increase from the crude value. When those without a parasite count were compared to the referent category, the adjusted OR was 15.5 (95% CI 1.31-183.14).

5.1.3 Risk factors for mortality determined by multivariable logistic regression

Three logistic models are shown in Table 5.3. The models were constructed first by adding age, as a categorical variable, then in a forward-stepwise manner other factors which are likely to influence the associations between age and mortality, such as study centre. These factors remained in the final model. Other factors not already included in the model were added as described in the methodology and if found to have significant Likelihood ratio tests, remained in the final model.

The first model, Model 1, used data from all one hundred cases whereas Model 2 was restricted to *definite* cases only. All *probable* cases survived and as a result the outcome, mortality, was restricted to *definite* cases hence the presentation of findings from the two models. In both models, adults were less at risk of death than children. The effect was more pronounced in Model 2. Quinine use before admission was identified as a risk factor when quinine was not given, and was significant in both models. Those cases that had seizures while on the ward were about 90% less likely to die than those who did not. A third model, Model 3, used only data for *definite* cases to fit the logistic regression. In addition to the factors identified by the previous models, this one identified parasite count as a risk factor. The parasite count when over 50,000 parasites/μL was associated with an eightfold increase in mortality compared to those with a lesser degree of parasitaemia. Those without counts were at even greater risk ($P = 0.05$). Adding parasite count to the model modified the ORs for mortality in Kapchorwa hospital as shown. The relative risk for mortality amongst the adult cases was even lower. Quinine given prior to admission became more protective.

Table 5.3: Risk factors for mortality by logistic regression

Risk factor	OR	Lower 95% CI	Upper 95% CI	LR Test*
Model 1 (N= 100)				
Aged ten years and above	0.51	0.09	2.86	0.43
Managed in Kapchorwa hospital	1.63	0.38	7.10	0.51
Quinine given prior to admission	0.14	0.02	1.23	**0.03**
Had seizures while on the ward	0.11	0.01	0.91	**0.01**
Model 2 (N=58)†				
Aged ten years and above	0.24	0.02	2.55	0.20
Managed in Kapchorwa hospital	3.92	0.44	35.36	0.20
Quinine given prior to admission	0.08	0.01	1.04	**0.02**
Had seizures while on the ward	0.05	0.01	0.48	**<0.001**
Model 3 (N=58)‡				
Aged ten years and above	0.11	0.01	1.50	0.07
Managed in Kapchorwa hospital	5.60	0.54	57.49	0.13
Quinine given prior to admission	0.04	0.00	1.12	**0.01**
Had seizures while on the ward	0.05	0.00	0.66	**0.01**
Parasite count				**0.04**
≤ 50,000 parasites/μL	1			
> 50,000 parasites/μL	8.36	0.86	80.84	
Missing info	25.03	0.98	636.18	

* Likelihood ratio test comparing models with the factor and without the factor
† Variables from Model 1 but restricted to *definite* cases
‡ Model fitted by adjusting for case definition at the onset

The three logistic models were a good fit of the data. The goodness-of-fit tests (Hosmer-Lemeshow test because of the small sample size) yielded the following results:

- Model 1: Hosmer-Lemeshow chi^2 (6 degrees of freedom) = 1.41, P = 0.96, 8 groups. Figure A in Appendix VI is a regression diagnostic plot of the Hosmer and Lemeshow influence (H-L dx^2) plotted for each case (as index numbers 1 to 100).
- Model 2: Hosmer-Lemeshow chi^2 (5 degrees of freedom) = 2.18, P = 0.82, 7 groups. Figure B in Appendix VI shows a diagnostic plot.
- Model 3: Hosmer-Lemeshow chi^2 (8 degrees of freedom) = 2.15, P = 0.95, 9 groups. Figure C in Appendix VI shows a diagnostic plot. This had better fit than the other two models.

Table C in the Appendix V summarises the results of Cox regression (time-to-event analysis) to show how they compared with the logistic models which do not take 'time-to-event' into account. The Cox models had similar findings to the logistic ones but with narrower confidence intervals.

5.2 Risk factors for early-onset neurological sequelae

The results here are derived from analyses of 23 cases with early-onset deficits of 90 cases who survived an episode of cerebral malaria. Univariate results are presented first. Bivariate and multivariate results follow.

5.2.1 Relative risk estimates determined by univariate analysis

Table B which gives the number of subjects with deficits and those without by categories of explanatory variable can be seen in Appendix V. The odds of having early-onset deficits are also presented. Table 5.4 summaries the findings from univariate comparisons of the odds to give crude odds ratios.

Table 5.4: Univariate odds ratios for early-onset neurological sequelae among patients who survived an episode of cerebral malaria. (N=90)

Variable	Coefficient	Standard error	P value	Odds ratio	Lower 95% CI	Upper 95% CI
Demographic & History information						
Centre (Mbale/Kapchorwa)	-0.1870	0.544	0.73	0.83	0.28	2.43
Age (less than 10 years/10 and above)	-0.1870	0.544	0.73	0.83	0.28	2.43
1-4 years				1		
5-9 years	0.8754	0.578	0.13	2.40	0.75	7.68
10 and above	0.1823	0.610	0.76	1.20	0.36	4.01
Seizures within 24 hours prior to admission (None/Any number)	1.2726	0.791	0.10	3.57	0.76	16.84
None				1		
1-3 seizures	1.1368	0.826	0.16	3.12	0.59	16.42
4-20 seizures	1.4469	0.841	0.08	4.25	0.76	23.87
Quinine given prior to admission (No/Yes)	1.0905	0.498	**0.03**	2.98	1.08	8.18
Previous medical admission to hospital (No/Yes)	0.7171	0.6304	0.25	2.05	0.59	7.16
Clinical examination on admission						
Able to localise painful stimuli at Level 2 (No/Yes)	-0.1147	0.546	0.83	0.89	0.30	2.62
Coma depth measured on Blantyre Coma Scale (cases aged 5 yrs and below)						
0-2	-0.3567	0.832	0.66	0.7	0.14	3.58
3-5				1		
No Score/Missing info	-	-	-	-	-	-
Coma depth measured on Glasgow Coma Scale (cases aged over 5 yrs)						
3-8	0.3747	0.697	0.59	1.45	0.37	5.71
9-12				1		
13-15	-	-	-	-	-	-
No Score/Missing info	0.9808	1.108	0.37	2.67	0.30	23.42
Has a stiff neck	0.7610	0.696	0.27	2.14	0.55	8.39
Body temperature						
35.0-38.5 °C				1		
38.6-39.4 °C	-0.5794	0.575	0.31	0.56	0.18	1.76
39.5-42.0 °C	-0.9361	1.118	0.40	0.39	0.04	3.62
Moderate – severe anaemia (No/Yes)	-0.1169	0.483	0.80	0.89	0.34	2.31
Clinical signs of jaundice (No/Yes)	0.1823	0.648	0.77	1.20	0.33	4.31
Clinical signs of moderate – severe dehydration (No/Yes)	-0.7719	1.108	0.48	0.46	0.05	4.13
Presence of extra heart sounds (No/Yes)						
None				1		
Yes	-1.6602	1.076	0.12	0.19	0.02	1.57
Missing info	-	-	-	-	-	-
Pulse pressure						
20-39 mmHg	0.2384	1.000	0.81	1.27	0.18	9.02
40-79 mmHg				1		
Missing info	0.8339	0.818	0.30	2.30	0.46	11.45

Table continued overleaf

Table 5.4 continued

Variable	Coefficient	Standard error	P value	Odds ratio	Lower 95% CI	Upper 95% CI
Respiratory abnormality (No/Yes)	-0.1715	0.493	0.72	0.84	0.31	2.23
Respiratory distress (Not likely/Likely)	-0.3342	1.145	0.77	0.71	0.07	6.85
Presence of Organomegaly (No/Yes)	1.1168	0.498	**0.03**	3.06	1.11	8.40
Enlarged spleen (No/Yes)	1.1119	0.556	0.05	3.04	0.99	9.34
Enlarged liver (No/Yes)	0.1431	0.592	0.81	1.15	0.36	3.71
In-hospital non-laboratory information						
First episode of witnessed seizures (none/any number)	0.1169	0.483	0.81	1.12	0.43	2.97
None				1		
1-3 seizures	-0.4810	0.600	0.42	0.62	0.19	2.03
4-20 seizures	0.9949	0.623	0.11	2.70	0.77	9.53
Seizure stoppage time						
1-2 days				1		
3-48 days	0.8109	0.760	0.28	2.25	0.49	10.37
Total seizure stoppage time						
1-2 days				1		
3-48 days	0.8159	0.528	0.12	2.26	0.78	6.52
Duration of unrousable coma						
Not in unrousable coma on admission				1		
For less than 48 hours	0.0645	0.617	0.91	1.07	0.31	3.62
For 48 hours or more	0.6286	0.624	0.31	1.88	0.54	6.54
Missing info	-	-	-	-	-	-
Coma recovery time						
1-2 days				1		
3-4 days	0.6286	0.672	0.35	1.88	0.49	7.17
5 and above	1.8971	0.769	**0.01**	6.67	1.24	35.90
Missing Info	-0.5306	0.926	0.56	0.59	0.09	3.72
Total coma recovery time						
1-2 days				1		
3-4 days	0.5108	0.787	0.51	1.67	0.35	7.97
5 and above	2.0369	0.714	**0.004**	7.67	1.63	36.09
Missing info	-	-	-	-	-	-
Fever clearance time						
1 day				1		
2-3 days	-0.9734	0.608	0.10	0.38	0.11	1.29
4-9 days	-0.4626	0.626	0.46	0.63	0.18	2.19
Missing info	0.6360	1.081	0.55	1.89	0.21	16.53
Total fever clearance time						
1 day				1		
2-3 days	-1.0986	0.611	0.07	0.33	0.10	1.15
4-15 days	-0.7884	0.587	0.18	0.45	0.14	1.48
Quinine loading dose prescribed on admission						
No				1		
Yes	-0.2776	1.182	0.81	0.76	0.07	7.82
Missing	-	-	-	-	-	-
Dose of quinine given on Day 0						
3-8.9 mg/kg	0.2513	0.899	0.78	1.29	0.22	7.50
9.0-10.9 mg/kg				1		
11.0-20.9 mg/kg	-0.4165	0.709	0.55	0.66	0.16	2.65
Missing info	-1.0191	0.614	0.09	0.36	0.11	1.20

Table continued overleaf

Table 5.4 continued

Variable	Coefficient	Standard error	P value	Odds ratio	Lower 95% CI	Upper 95% CI
Duration of hospital stay						
Less than 6 days	-0.5520	0.636	0.38	0.58	0.17	2.00
6 to 8 days				1		
More than 8 days	1.1527	0.628	0.06	3.17	0.92	10.86
Laboratory based information						
Random blood glucose on admission (>2.2/≤2.2 mmol/L)	-0.0323	0.854	0.97	0.97	0.18	5.22
Less than 5 mmol/L	0.5390	0.698	0.44	1.71	0.44	6.74
5 – 6.9 mmol/L				1		
7 and above	1.0986	0.666	0.10	3.0	0.81	11.08
Missing info	-0.5596	0.794	0.48	0.57	0.12	2.71
Parasite count						
50,000 parasites/μL and below				1		
> 50,000 parasites/μL	0.2364	0.533	0.65	1.27	0.44	3.63
Missing info	0.0540	0.744	0.94	1.06	0.24	4.60
Parasite clearance time						
1 day				1		
2 days	-0.9555	0.612	0.11	0.38	0.11	1.32
3-4 days		0.715	1.00	1.00	0.24	4.13
Missing info	-0.6061	0.748	0.41	0.55	0.12	2.43
Haemoglobin concentration						
3.0-9.9 g/dL	-0.4339	0.553	0.43	0.65	0.22	1.92
10.0-15.0 g/dL				1		
Missing info	-1.2040	0.668	0.07	0.30	0.08	1.11
HIV infection						
No				1		
Yes	0.4055	1.241	0.74	1.50	0.13	17.83
Missing	1.0186	0.610	0.09	2.77	0.81	9.43
Serum Sodium concentration						
<135 mmol/L	0.7963	0.876	0.36	2.22	0.40	12.37
135-146 mmol/L				1		
>146 mmol/L	1.2237	1.122	0.27	3.40	0.38	30.66
Missing info	1.6139	0.825	0.05	5.02	1.00	25.32
Serum Calcium concentration						
<2 mmol/L	0.4308	1.295	0.73	1.54	0.12	19.47
2-3 mmol/L				1		
>3 mmol/L	1.0217	1.164	0.38	2.78	0.28	27.21
Missing info	1.7525	1.097	0.11	5.77	0.67	49.61
Serum Chloride concentration						
<95 mmol/L	0.8473	1.573	0.59	2.33	0.11	50.98
95-105 mmol/L				1		
>105 mmol/L	0.4054	1.159	0.72	1.50	0.15	14.57
Missing info	1.2867	1.115	0.24	3.62	041	32.22
White blood cell count						
2000-4700 cells/L	2.0005	0.852	**0.02**	7.39	1.39	39.27
4701-6700 cells/L				1		
6701-27000 cells/L	1.6802	0.867	**0.05**	5.37	0.97	29.40
Missing info	1.3437	0.900	0.13	3.83	0.65	22.37

Patients seen at Kapchorwa hospital had a similar probability of having deficits at discharge when compared with those seen at Mbale hospital (OR 0.83 [95% CI 0.28-2.43]). Likewise children aged 10 years and above had fairly similar chances of having early deficits. When smaller age groups were used, children aged 5 to 9 years were just over twice (OR 2.40 [95% CI 0.75-7.68]) as likely to have deficits compared to those aged below 5 years. Those aged 10 and above when compared to those less than 5 had an OR of 1.20 (95% CI 0.36-4.01). A history of any number of seizures in the 24 hours prior to admission was associated with a greater likelihood of deficits compared to a negative history for seizures (OR 3.57 [95% CI 0.76-16.84). The relative risk for deficits increased with increasing number of seizures (P = 0.09 for test of trend). Those who had between 4-20 seizures prior to admission having 4 times the potential for sequelae compared to those without (P = 0.09) and those who had between 1-3 seizures having 3 times the same potential (P = 0.17). Cases that were given quinine prior to admission were almost 3 times more likely to have early deficits than those that did not receive quinine prior to admission (P = 0.03). Cases that had been admitted to hospital before were at greater risk of deficits OR 2.05 (95% CI 0.59-7.16).

Patients with a greater degree of unconsciousness as indicated by the inability to localise pain did not seem to be at greater risk of developing deficits. Using the two coma scales the effect of knowing the depth of coma was assessed. With the Blantyre Coma Score (n=42), those that scored 0-2 and 3-5 had fairly similar magnitudes of risk. None of the six cases who were not scored developed deficits. On the Glasgow coma scale (n=48), those in the lowest category 3-8, were 45% more likely to be at risk compared to those with scores 9-12. It was not possible to use the higher category as the referent one because none of the five cases in this group, who were classified as *probable* cases, developed deficits. Increasing levels of body temperature appeared to be protective when compared to those with temperatures between 35°C and 38.5°C. The odds ratio for those in the 38.5-39.4°C category was 0.56 (95% CI 0.18-1.76) and was 0.39 (95% CI 0.04-3.62) for those with hyperthermia, i.e. a core temperature of 40°C and above (core body temperature is equal to temperature taken in axilla plus 0.5°C). The presence of moderate to severe anaemia was associated with a smaller relative risk for sequelae compared to those without (OR 0.89 [95% CI 0.34-2.31]) but the presence of jaundice had the

opposite effect; those with jaundice having a higher OR of 1.2 (95% CI 0.33 4.31) than those without. Cases who did not have clinical signs of moderate to severe dehydration were about 50% more likely to develop deficits compared to those with signs of moderate to severe dehydration (P value was not significant). The detection of extra heart sounds appeared to decrease the relative risk of deficits (OR 0.19 [95% CI 0.02-1.57]) probably not a directly related process but a proxy indication of the influence of a doctor who was around to auscultate the heart and in so doing provide additional medical support. None of the cases had clinical signs suggestive of shock. Using the pulse pressure category of 40-79 mmHg as the referent group the relative risk for deficits was 1.27 (95% CI 0.18-9.02) when the pulse pressure was between 20-39 mmHg and 2.30 (95% CI 0.46-11.45) when blood pressure was not measured. The presence of any respiratory abnormality or the presence of respiratory distress were associated with a reduction in the risk of deficits compared to the absence of the feature (OR 0.84 [95% CI 0.31-2.23] and 0.71 [95% CI 0.07-6.85] respectively). Organomegaly on the other hand was associated with a 3 fold increase in relative risk (P = 0.03). An enlarged spleen was responsible for the effect of organomegaly.

Comparing the number of seizures showed that those with 4 or more seizures during the first episode of witnessed seizures were more than 2 times likely to have deficits compared to those who did not have seizures. Those who had 1-3 seizures were less likely to have deficits compared to those without. Comparing those with 4 or more seizures, with those with less than 4 seizures resulted in an OR of 4.38 (95% CI 0.99-19.43), further illustrating the trend of increased risk with a greater number of seizures. The correlation between number of seizures within 24 hours before admission and number of witnessed seizures on the first episode was 43% which was not a high correlation. The duration taken to control the seizures (i.e. seizure stoppage time) showed that having seizures for 3 or more days increased the potential for deficits two fold (95% CI 0.49-10.37) compared to less than 3 days. The relative risk (OR 2.26 [95% CI 0.78-6.52]) remained similar when the number of days for which the subject was reported to have had seizures were added to the number of days with witnessed seizures (i.e. total seizure stoppage time).

Cases in unrousable coma for less than 48 hours did not differ in their potential for deficits when compared with those not in unrousable coma (i.e. unconscious but able to localise pain). However those who were in coma for 48 hours or more were about 2 times more likely to have deficits than the same referent group (OR 1.88 [95% CI 0.54-6.54]) or if the referent group was unrousable coma for less than 48 hours (OR 1.76 [95% CI 0.55-5.61]). The coma recovery time, which is obtained by using the coma scales showed similar findings. Those in coma for 5 days and more, had a relative risk of 6.67 ($P = 0.01$) compared to those in coma for 1 to 2 days. The relative risk increased in a stepwise fashion with increasing categories of coma recovery time except when information was missing ($P = 0.01$ for test for trend excluding category with missing values). When the reported number of days in coma prior to admission were added, patients in coma for 5 days or more had a relative risk of 7.67 compared to those in coma for 1 to 2 days ($P < 0.001$). The test for trend using this variable was also statistically significant ($P = 0.04$). A fever clearance time of 1 day was used as the referent group to estimate the relative risk of having a fever for 2 to 3 days and 4 to 9 days. The odds ratios respectively were 0.38 (95% CI 0.11-1.29) and 0.63 (95% CI 0.18-2.19). The risk for deficits was greater when information on the duration of fever was missing. The total fever clearance time showed a similar trend even though all cases contributed information.

Cases who received a loading dose of quinine on admission had about 20% less potential for deficits compared to those without such a prescription. None of the cases without this information developed early deficits. The higher amounts of quinine in contrast, 570-1800 mg of quinine given on Day 0, were associated with an OR of 1.16 (95% CI 0.42-3.15) compared to the lower category of 225-569 mg. Cases in whom this information was not available when compared to the lower category had an OR of 0.19 (95% CI 0.02-1.74). Of the forty-four cases with information that allowed quinine dosage to be calculated i.e. quinine amount by body weight per dose, those given 3 to 8.9 mg/kg (n=7) compared to those given 9 to 10.9 mg/kg (n=19) had a relative risk of 1.29 (95% CI 0.21-7.79). Those given 11 to 20 mg/kg (n=18) had a relative risk of 0.66 (95% CI 0.16-2.72) compared to those in the referent group. Those without sufficient information to calculate the dosage (n=56) also had a smaller risk (OR 0.36 [95% CI 0.10-1.25]) compared with the referent group. The target duration of hospital stay was 7 days. The duration of 6 to

8 days of hospital stay was used as the referent group to estimate the relative risk of deficits in those who spent less or more than this duration. Those who spent less than 6 days had an OR of 0.58 (95% CI 0.17-2.00) and those who spent more than 8 days had an OR of 3.17 (95% CI 0.92-10.86).

The study was not able to detect an association between hypoglycaemia and early-onset sequelae. Cases with random blood glucose concentration in the lower category as shown in the table had a relative risk of 1.71 (95% CI 0.44-6.74) compared to those in the middle category (5-6.9 mmol/L). Those with concentrations over 7 mmol/L had an even greater risk estimate of 3.0 (95% CI 0.81-11.08) compared with the middle category (P = 0.10). Cases without blood glucose estimates were at less risk with an OR of 0.57 (95% CI 0.12-2.71). A parasite count over 50,000 parasites/μL was associated with a slightly greater likelihood for deficits than parasite counts below that degree. There was little difference when those without counts were compared with the lower degree of parasitaemia. The parasite clearance time did not show a trend in relative risk. The odds of deficits among cases with the lower category of haemoglobin concentration, 3.0-9.9g/dL, was compared with the odds of deficits among cases with Hb concentrations between 10.0 and 15.0 g/dL. The odds ratio obtained was 0.65 (95% CI 0.22-1.92). Few cases tested HIV-1 positive however the relative risk for deficits was greater among them than the negative cases. Those who were not tested also had a greater relative risk compared with the seronegative cases.

There was a general trend in the relative risk for deficits when the normal range of the serum concentrations of the three electrolytes were compared with concentrations either below or above. The out of normal ranges were associated with greater potential for deficits as shown by the larger ORs in each comparison. These trends were statistically significant for sodium (P = 0.02) and calcium (P = 0.02) but not for chloride (P = 0.1). The estimates of relative risks increased when the lower and upper categories of total white blood cell count were compared with the middle one. Cases with counts below 4,700 cells/L were about 7 times more at risk than those with counts between 4701 and 6700 cells/L (P = 0.02). Those with counts over 6700 cells/L were about 5 times more at risk than the same referent group (P =

0.05). Cases lacking information on white cell count were almost 4 times more at risk (P = 0.14).

5.2.2 Adjusted relative risk estimates determined with bivariate analysis

The adjusted odds ratios for early onset neurological deficits are summarised in Table 5.5 below. The relative risk estimates for age as 3 categories when controlled for case definition caused the crude ORs to increase in magnitude. This effect was greater when centre was adjusted for. The risk for deficits if there was a history of seizures within 24 hours before admission did not differ even when controlled for differences in case definition, study centre or age group. However when the actual numbers of seizures reported were considered the relative risks showed an increasing trend. Controlling for case definition, the magnitude of the risk estimates were less extreme, i.e., tending towards one, with an OR of 2.90 (95% CI 0.55-15.35) if the number of seizures were 1-3 and 3.21 (95% CI 0.53-19.44) if the number of seizures were 4-20. The unadjusted OR and the trend with number of seizures were not modified by study site or age group. The risk of deficits was two times greater if there was a previous history of admission irrespective of case definition, centre or age group. There was a change in the direction of the risk among cases who were unable to localise pain when case definition was taken into account. Whereas the unadjusted OR was less than one, it increased above one to 1.82 (95% CI 0.42-7.78) when adjusted for case definition but not when adjusted for centre or age. Cases who scored in the lower category of coma depth in the Blantyre and Glasgow coma scales had opposite chances of developing deficits as shown by the ORs. However, those who were not scored on either scale were less likely to develop deficits when compared to the referent group as shown in the table.

Table 5.5: Adjusted Odds ratios for early-onset neurological sequelae

Risk factor	Unadjusted OR	Variable adjusted for: Case definition OR	Case definition 95% CI	Centre OR	Centre 95% CI	Age group OR	Age group 95% CI
Factors shown to have differences in the descriptive analyses							
Centre							
Mbale	1	1		NA	-	1	
Kapchorwa	0.83	0.89	*0.31-2.55*	-	-	0.86	*0.29-2.54*
Age group 1							
≤ 10 yrs	1	1		1		1	
> 10 years	0.83	0.88	*0.30-2.62*	0.86	*0.29-2.54*	NA	-
Age group 2							
1-4 yrs	1	1		1		NA	-
5-9 yrs	2.40	2.94	*0.86-10.06*	3.00	*0.76-11.86*	-	-
10 yrs and above	1.20	1.51	*0.42-5.42*	1.58	*0.40-6.23*	-	-
Seizures within 24 hours before admission	3.57	3.12	*0.63-15.56*	3.57	*0.71-18.00*	3.57	*0.71-18.00*
Number of seizures within 24 hours prior to admission							
None	1	1		1		1	
1-3 seizures	3.12	2.90	*0.55-15.35*	3.18	*0.59-17.21*	3.09	*0.57-16.70*
4-20 seizures	4.25	3.21	*0.53-19.44*	4.25	*0.65-27.89*	4.69	*0.74-29.83*
Admitted to hospital before	2.05	2.10	*0.57-7.67*	2.02	*0.55-7.40*	1.98	*0.59-6.68*
Unable to localise painful stimuli	0.89	1.82	*0.42-7.78*	0.89	*0.30-2.61*	0.92	*0.31-2.75*
Blantyre Coma Score§							
0-2	0.7	-	-	0.78	*0.15-4.11*	0.82	*0.16-4.15*
3-5	1	1		1		1	
Missing info	0.76	0.64	*0.14-2.97*	0.75	*0.15-3.67*	0.82	*0.16-4.15*
Glasgow Coma Score**							
3-8	1.45	2.70	*0.36-20.22*	1.39	*0.31-6.29*	1.38	*0.35-5.45*
9-12	1	1		1		1	
13-15	-	-	-	-	-	-	-
Missing info	0.84	0.79	*0.24-2.54*	0.42	*0.07-2.45*	0.52	*0.10-2.62*
Has a stiff neck	2.14	2.06	*0.58-7.25*	2.30	*0.55-9.61*	2.30	*0.55-9.61*
Body temperature							
35.0-38.5 °C	1	1		1		1	
38.6-39.4 °C	0.56	0.47	*0.16-1.40*	0.56	*0.18-1.79*	0.56	*0.18-1.77*
39.5-42.0 °C	0.39	0.21	*0.02-2.45*	0.39	*0.04-3.74*	0.39	*0.04-3.75*
Presence of moderate to severe anaemia	0.89	0.79	*0.31-2.04*	0.86	*0.32-2.27*	0.84	*0.32-2.22*
Presence of jaundice	1.20	1.17	*0.32-4.35*	1.15	*0.31-4.33*	1.15	*0.31-4.33*

Table continued overleaf

§ Children aged 5 years and below
** Children aged over 5 years

Table 5.5 continued

Risk factor	Unadjusted OR	Variable adjusted for: Case definition OR	Case definition 95% CI	Centre OR	Centre 95% CI	Age group OR	Age group 95% CI
Presence of any respiratory abnormality	0.84	0.74	*0.27-2.05*	0.79	*0.28-2.18*	0.75	*0.27-2.08*
Presence of any extra heart sounds							
No	1	1		1		1	
Yes	0.19	0.21	*0.03-1.56*	0.17	*0.02-1.62*	0.16	*0.02-1.48*
Presence of organomegaly	3.06	2.83	*1.00-8.04*	2.95	*1.11-7.82*	3.02	*1.09-8.32*
Presence of enlarged spleen	3.04	2.78	*0.87-8.90*	3.07	*0.96-9.82*	3.06	*0.96-9.71*
Pulse rate							
50-84 beats/min	1	1		1		1	
85-119 beats/min	3.60	3.17	*0.76-13.23*	3.39	*0.82-14.00*	3.60	*0.88-14.61*
120-154 beats/min	2.00	2.01	*0.42-9.60*	1.91	*0.47-7.77*	1.31	*0.25-6.89*
Respiratory rate							
10-29	1	1		1		1	
30-49	2.67	2.42	*0.68-8.67*	2.62	*0.75-9.09*	3.12	*0.70-14.02*
50-90	1.38	1.30	*0.16-10.84*	1.12	*0.19-6.75*	1.75	*0.14-21.62*
Pulse pressure							
20-39 mmHg	1.27	0.91	*0.14-6.05*	0.79	*0.10-6.14*	0.73	*0.09-5.84*
40-79 mmHg	1	1		1		1	
Missing info	2.30	1.40	*0.33-5.86*	2.01	*0.42-9.61*	2.40	*0.49-11.68*
Had witnessed seizures	1.12	0.88	*0.33-2.38*	1.10	*0.42-2.90*	1.11	*0.43-2.90*
Number of witnessed seizures on first episode							
None	1	1		1		1	
1-3 seizures	0.62	0.55	*0.17-1.72*	0.61	*0.18-2.11*	0.62	*0.19-2.03*
4-20 seizures	2.70	1.99	*0.51-7.85*	2.67	*0.77-9.27*	2.86	*0.78-10.53*
Fever clearance time							
1 day	1	1		1		1	
2-3 days	0.38	0.39	*0.12-1.29*	0.38	*0.11-1.29*	0.34	*0.10-1.23*
4-9 days	0.63	0.45	*0.11-1.86*	0.71	*0.18-2.82*	0.73	*0.19-2.72*
Missing info	1.89	3.00	*0.22-40.05*	1.85	*0.24-14.30*	1.87	*0.21-17.07*
Was given a loading dose of quinine on admission	0.76	0.37	*0.04-3.78*	0.43	*0.04-4.07*	0.46	*0.06-3.31*
Has hypoglycaemia	0.97	0.99	*0.18-5.32*	0.94	*0.17-5.21*	0.94	*0.17-5.21*
Random blood glucose							
< 5 mmol/L	1.71	0.60	*0.15-2.50*	0.59	*0.15-2.35*	1.03	*0.22-4.92*
5-6.9 mmol/L	1	1		1		1	
≥7 mmol/L	3.00	1.70	*0.45-6.49*	1.57	*0.40-6.18*	1.72	*0.47-6.26*
Missing info	0.57	0.34	*0.07-1.73*	0.40	*0.08-1.95*	0.35	*0.08-1.57*
Haemoglobin concentration							
3.0-9.9 g/dL	0.65	0.65	*0.22-1.93*	0.65	*0.21-1.98*	0.66	*0.21-2.04*
10.0-15.0 g/dL	1	1		1		1	
Missing info	0.30	0.31	*0.08-1.25*	0.29	*0.07-1.17*	0.28	*0.07-1.15*
White blood cell count							
2,000-4,700	7.39	7.27	*1.18-44.74*	7.35	*1.19-45.59*	9.05	*1.19-68.94*
4,701-6,700	1	1		1		1	
6,701-27,000	5.37	4.99	*0.78-31.97*	5.82	*0.86-39.18*	4.69	*0.82-26.65*
Missing info	3.83	3.24	*0.48-22.09*	3.33	*0.51-21.82*	3.78	*0.60-24.06*

Table continued overleaf

Table 5.5 continued

Risk factor	Unadjusted OR	Variable adjusted for: Case definition OR	Case definition 95% CI	Centre OR	Centre 95% CI	Age group OR	Age group 95% CI
Other explanatory factors							
Quinine given prior to admission	2.98	3.02	*1.08-8.46*	2.99	*1.08-8.28*	3.03	*1.09-8.45*
Duration taken to localise pain							
Localises pain on admission	1	1		1		1	
≤ 48 hours	1.07	0.67	*0.06-7.16*	1.06	*0.34-3.35*	1.06	*0.31-3.63*
> 48 hours	1.88	1.11	*0.09-13.30*	1.83	*0.54-6.21*	1.85	*0.52-6.54*
Coma recovery time							
1-2 days	1	1		1		1	
3-4 days	1.88	2.25	*0.48-10.61*	1.86	*0.48-7.15*	1.99	*0.52-7.61*
5 and above	6.67	6.33	*1.15-34.93*	6.40	*1.14-35.78*	6.57	*1.20-36.01*
Missing Info	0.59	0.64	*0.12-3.28*	0.51	*0.07-3.63*	0.57	*0.09-3.77*
Total coma recovery time							
1-2 days	1	1		1		1	
3-4 days	1.67	1.81	*0.35-9.38*	1.72	*0.39-7.56*	2.44	*0.47-12.58*
5 and above	7.67	6.96	*1.39-34.97*	7.43	*1.58-34.92*	7.36	*1.52-35.65*
Dose of quinine given on Day 0							
3-8.9 mg/kg	1.29	1.29	*0.22-7.68*	1.34	*0.22-8.01*	1.43	*0.21-9.86*
9.0-10.9 mg/kg	1	1		1		1	
11.0-20.9 mg/kg	0.66	0.60	*0.14-2.62*	0.67	*0.16-2.75*	0.64	*0.15-2.81*
Missing info	0.36	0.47	*0.14-1.60*	0.36	*0.11-1.26*	0.38	*0.11-1.32*
Duration of hospital stay							
< 6 days	0.58	0.61	*0.17-2.21*	0.55	*0.16-1.91*	0.58	*0.16-2.09*
6-8 days	1	1		1		1	
> 8 days	3.17	3.82	*1.00-14.62*	3.44	*0.89-10.94*	3.12	*0.89-10.94*
Parasite count							
≤ 50,000 parasites/μL	1	1		1		1	
> 50,000 parasites/μL	1.27	1.29	*0.45-3.73*	1.36	*0.43-4.24*	1.23	*0.43-3.52*
Missing info	1.06	2.01	*0.41-9.98*	0.91	*0.20-4.13*	1.06	*0.26-4.29*
Parasite clearance time							
1 day	1	1		1		1	
2 days	0.38	0.34	*0.08-1.36*	0.37	*0.10-1.30*	0.36	*0.10-1.24*
3-4 days	1.00	1.09	*0.24-4.85*	1.12	*0.26-4.86*	0.90	*0.23-3.55*
Missing info	0.55	1.48	*0.34-6.54*	0.53	*0.11-2.50*	0.58	*0.14-2.47*

Table continued overleaf

Table 5.5 continued

Risk factor	Unadjusted OR	Variable adjusted for: Case definition OR	Case definition 95% CI	Centre OR	Centre 95% CI	Age group OR	Age group 95% CI
HIV infection							
No	1	1		1		1	
Yes	1.50	2.75	0.12-63.16	1.92	*0.15-24.60*	3.12	*0.04-229.46*
Missing	2.77	2.85	0.82-9.98	3.46	*0.92-13.11*	3.05	*0.84-11.03*
Serum Sodium concentration							
<135 mmol/L	2.22	2.04	*0.47-8.82*	1.97	*0.44-8.85*	2.31	*0.38-13.88*
135-146 mmol/L	1	1		1		1	
>146 mmol/L	3.40	2.86	*0.40-20.37*	3.57	*0.46-27.86*	3.50	*0.33-37.66*
Missing info	5.02	5.24	*0.91-30.10*	3.69	*0.94-14.48*	6.35	*0.95-42.18*
Serum Calcium concentration							
<2 mmol/L	1.54	0.67	*0.04-11.38*	2.86	*0.19-42.53*	1.09	*0.08-15.69*
2-3 mmol/L	1	1		1		1	
>3 mmol/L	2.78	1.83	*0.19-17.66*	3.85	*0.35-42.46*	2.50	*0.22-28.74*
Missing info	5.77	6.35	*0.55-73.04*	5.29	*0.52-53.91*	5.52	*0.62-49.03*
Serum Chloride concentration							
<95 mmol/L	2.33	2.00	*0.13-31.98*	4.00	*0.07-218.59*	1.67	*0.06-45.44*
95-105 mmol/L	1	1		1		1	
>105 mmol/L	1.50	1.20	*0.13-11.32*	1.00	*0.09-11.04*	1.58	*0.15-17.05*
Missing info	3.62	3.40	*0.44-26.46*	3.60	*0.38-34.11*	3.49	*0.37-32.40*

Cerebral malaria with moderate to severe anaemia was less likely to predispose to early-onset deficits than cerebral malaria only. This finding remained even after adjusting for case definition, centre or age. The presence of jaundice had the opposite effect. Higher pulse rates and higher respiratory rates when compared with the lower categories had a greater relative risk even when adjusted for the three factors separately. The pulse and respiratory rates had a correlation coefficient of 0.32. Controlling for case definition altered the direction of the relative risk when those with witnessed convulsions were compared to those without. Cases who had 1-3 witnessed seizures had less probability for deficits compared to those without seizures even when controlled for case definition or age. However, when the number of seizures was over 4, the relative risk was greater when controlled for any of the three factors although less so when controlled for case definition. The adjusted ORs for fever clearance times were not modified significantly, however when no information was collected on temperature, the OR increased significantly almost doubling when adjusted for case definition. The risk of deficits was 0.43 (95% CI 0.04-4.07) when a loading dose of quinine was given and study site taken into account. This differed slightly from the unadjusted value and was similar when adjusted for age. Adjusting for case definition made the risk more extreme, i.e. away from one.

The adjusted risk estimates for the three comparison categories of random blood glucose were less than the unadjusted values. Those for the two comparison categories for Hb did not differ from the unadjusted ones. Cases with parasite counts over 50,000 parasites/μL continued to have a risk estimate close to the unadjusted value (OR 1.27) when adjusted for case definition, or the other two factors. When those without parasite counts were compared with the referent group, the adjusted OR doubled to 2.01 (95% CI 0.41-9.98) when adjusted for case definition but not for the other factors. The same effect occurred with the parasite clearance time. Kapchorwa cases were not assessed for HIV, therefore the OR adjusted for centre, comparing HIV sero-positives with sero-negatives was different from the unadjusted estimate which took all cases into account. The estimate was even greater when age was controlled for (OR 3.12 [95% CI 0.04-229.46) although the confidence intervals were very wide.

5.2.3 Risk factors for early-onset sequelae determined by multivariable logistic regression

Multivariable analyses as described previously were conducted to test the hypothesis that age of onset of cerebral malaria is related with early-onset sequelae and to elucidate any risk factors for the outcome. First age was used as two categories (Models 1a and 1b in Table 5.6) and then as three categories (Models 2a and 2b in Table 5.7). It was possible to use both age groups at this level because the frequency of the outcome, early-onset deficits, was greater than the frequency of outcome, mortality, in the previous analyses.

As shown in Table 5.6, the factors that were significantly associated with greater potential for early-onset sequelae were quinine given prior to admission, coma recovery time for subjects aged 5 years and above, and the presence of organomegaly. Those factors which were significantly associated with less risk were total fever clearance time for more than 1 day, and Hb concentrations between 3 and 9.9 g/dL. Adults were at less risk for deficits in Models 1a and 2a but when age was in three categories there was a reversal of the risk estimates. Cases that received quinine prior to admission had a fourfold chance of getting early deficits. This finding was fairly constant in all the models although the effect of controlling for case definition further increased its magnitude. A coma recovery time between 1 and 2 days was used as the referent group to determine the relative risk for greater durations of coma. Controlling for the other variables in Model 1a, the OR was 3.10 (95% CI 0.56-17.19) when the duration was between 3-4 days, and 22.81 (95% CI 2.69-193.71) when the duration was 5 days and more. Cases without information on coma duration were at less risk than the referent group. The effect of using the other age grouping modified the risk estimates as shown. Organomegaly when present was a risk factor as illustrated in all the models. The OR was greater when the case definition was included in the model resulting in a tenfold probability for deficits.

Table 5.6: Risk factors for early-onset deficits by logistic regression (N=90)

Risk factor	OR	Lower 95% CI	Upper 95% CI	LR test††
Model 1a				
Aged 10 years and above	0.79	0.18	3.50	0.75
Managed in Kapchorwa	0.54	0.12	2.44	0.41
Quinine given prior to admission	4.51	1.20	17.00	**0.02**
Coma recovery time				**0.01**
1-2 days	1			
3-4 days	3.10	0.56	17.19	
5 and above	22.84	2.69	193.71	
Missing Info	0.90	0.08	9.65	
Total fever clearance time				**0.002**
1 day	1			
2-3 days	0.07	0.01	0.42	
4-15 days	0.11	0.02	0.61	
Haemoglobin concentration				**0.01**
3.0-9.9 g/dL	0.27	0.06	1.27	
10.0-15.0 g/dL	1			
Missing info	0.07	0.01	0.45	
Has organomegaly	6.16	1.40	27.06	**0.01**
Model 1b‡‡				
Age group				0.14
1-4 yrs	1			
5-9 yrs	6.92	0.88	54.29	
10 yrs and above	2.23	0.33	15.06	
Managed in Kapchorwa	0.29	0.05	1.60	0.13
Quinine given prior to admission	4.69	1.20	18.40	**0.02**
Coma recovery time				**0.003**
1-2 days	1			
3-4 days	2.47	0.43	14.22	
5 and above	21.43	2.48	185.33	
Missing Info	0.38	0.02	6.42	
Total fever clearance time				**0.01**
1 day	1			
2-3 days	0.09	0.01	0.58	
4-15 days	0.14	0.02	0.81	
Haemoglobin concentration				**0.04**
3.0-9.9 g/dL	0.39	0.07	2.04	
10.0-15.0 g/dL	1			
Missing info	0.10	0.01	0.69	
Has organomegaly	10.44	1.84	59.21	**0.002**

†† Likelihood ratio test comparing the model with the factor and without the factor
‡‡ Using age in three categorises

Table 5.7: Risk factors for early-onset deficits by logistic regression and adjusting for case definition (N=90)

Risk factor	OR	Lower 95% CI	Upper 95% CI	LR test§§
Model 2a* **				
Aged 10 years and above	0.84	0.19	3.71	0.81
Managed in Kapchorwa	0.65	0.14	3.06	0.57
Quinine given prior to admission	4.65	1.23	17.58	**0.02**
Coma recovery time				**0.01**
1-2 days	1			
3-4 days	2.41	0.37	15.54	
5 and above	20.42	2.38	175.32	
Missing Info	0.99	0.09	10.81	
Total fever clearance time				**0.002**
1 day	1			
2-3 days	0.06	0.01	0.39	
4-15 days	0.11	0.02	0.61	
Haemoglobin concentration				**0.01**
3.0-9.9 g/dL	0.26	0.05	1.25	
10.0-15.0 g/dL	1			
Missing info	0.08	0.01	0.50	
Has organomegaly	5.93	1.35	26.12	**0.01**
Model 2b†††				
Age group				0.12
1-4 yrs	1			
5-9 yrs	7.88	0.98	63.35	
10 yrs and above	2.71	0.38	19.57	
Managed in Kapchorwa	0.35	0.06	1.97	0.21
Quinine given prior to admission	5.13	1.28	20.63	**0.02**
Coma recovery time				**0.01**
1-2 days	1			
3-4 days	1.68	0.25	11.33	
5 and above	17.41	2.01	150.57	
Missing Info	0.41	0.02	7.51	
Total fever clearance time				**0.01**
1 day	1			
2-3 days	0.07	0.01	0.49	
4-15 days	0.14	0.02	0.81	
Haemoglobin concentration				0.06
3.0-9.9 g/dL	0.39	0.07	2.09	
10.0-15.0 g/dL	1			
Missing info	0.12	0.02	0.78	
Has organomegaly	10.43	1.79	60.72	**0.003**

§§ Likelihood ratio test comparing the model with the factor and without the factor
*** Adjusted for case definition
††† Adjusted for case definition and using age categories into three groups

The results of goodness-of-fit tests (using the Hosmer-Lemeshow test) are as follows:

- Model 2a: H-L chi^2 (8 degrees of freedom) = 3.55, P = 0.89, 10 groups. Figure E in Appendix VI shows a diagnostic plot
- Model 2b: H-L chi^2 (8 degrees of freedom) =1.61, P = 0.99, 10 groups.
- Model 1b: H-L chi^2 (8 degrees of freedom) = 4.78, P = 0.78, 10 groups.
- Model 1a: H-L chi^2 (8 degrees of freedom) = 7.70, P = 0.46, 10 groups. Figure D in Appendix VI is a diagnostic plot for the model.

The results show that the logistic models were appropriate for the data.

5.3 Risk factors for late-onset neurological sequelae

The results presented here are from survival analyses consisting of 90 survivors of cerebral malaria of whom 52 attended follow-up and 19 had late-onset sequelae. Survivors are considered as two groups, children and adults in order to determine any differences between both in terms of the rates of deficits.

5.3.1 The incidence rates of late-onset deficits amongst children and adult survivors of cerebral malaria stratified by explanatory variables.

Twelve children and seven adults were classified as having late-onset neurological sequelae. Their Kaplan-Meier 'survival' estimates are illustrated in Figure 5.1. The 'events' for these time-to-event analyses are the late-onset deficits, i.e. a subject 'fails' if a deficit is detected and a subject 'survives' if no deficit is detected at the time of assessment. The analysis time is the period from discharge to the detection of late-onset deficits and is variable from one subject to the other (although there were targets for the period between discharge and follow-up visits as described in the methodology). The figure does not appear to show any consistent difference between the two groups (P = 0.99 from the log-rank test). The incidence rate of deficits in children during the study period was 2.45 deficits per person-year compared to a rate in adults of 2.16 deficits per person-year. Table 5.8 contains the incidence rates of deficits in children and adults stratified by explanatory factors. The incidence rate ratios comparing rates between children and adults are also given. The table shows that children had a higher incidence of late-onset sequelae in Kapchorwa than Mbale.

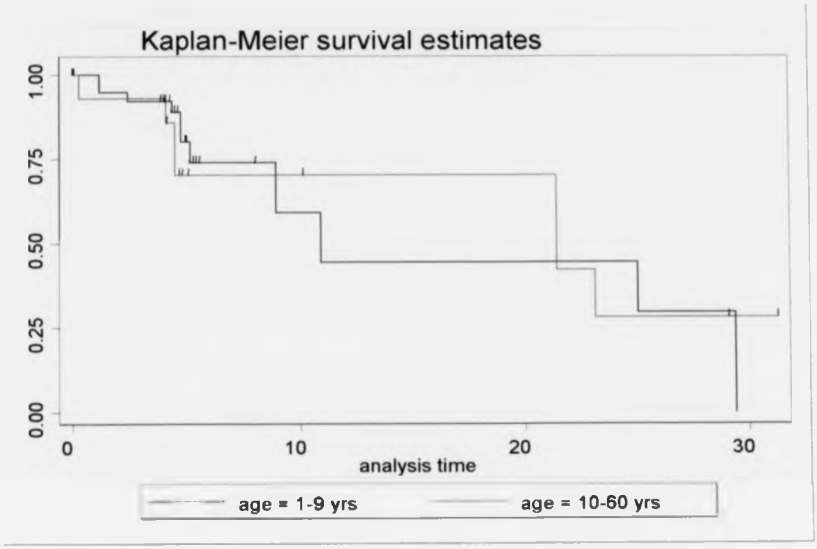


Figure 5.1: Kaplan Meier 'survival' curves showing the probability of not having late-onset sequelae during the follow-up period (analysis time) in weeks for child (1-9 yrs) and adult (10-60 yrs) survivors who attended follow up visits (N=90).

Adult cases in Kapchorwa had a higher frequency of deficits than children (IRR=1.21 [95% CI 0.29-5.82]). Children that did not have a history of seizures within 24 hours before admission had a higher rate of deficits than adults without histories of reported seizures. However, when a history of 1 to 3 seizures was given, the incidence of deficits was greater in adults. A greater number of seizures was associated with a higher incidence of sequelae in children (IRR=0.62 [95% CI 0.06-3.79]). Adult cases with a previous history of admission before the current illness had an incidence rate of 11.69 deficits per person-year. Child cases with a similar history had a rate of 2.25 deficits per person-year. Survivors who on admission could localise pain were more likely to have deficits if they were adults than children, (IRR=4.11 [95% CI 0.09-36.74])

Table 5.8: Summary of the stratified incidence rates and rate ratios for late-onset neurological deficits amongst child and adult survivors of cerebral malaria who attended follow-up (n=52)

Variable	Children			Adults			Incidence rate ratio (Adults / Children)	Lower 95% CI	Upper 95% CI
	No. of events	Discharge to 1st visit (person years)*	Incidence rate (per person-year)	No. of events	Discharge to 1st visit (person years)	Incidence rate (per person-year)			
Overall	12	4.88	2.46	7	3.23	2.16	0.88	0.29	2.43
Demographic & History information									
Centre									
Mbale	8	2.50	3.21	1	0.27	3.76	1.18	0.27	8.80
Kapchorwa	4	2.39	1.67	6	2.97	3.02	1.21	0.29	5.82
Seizures within 24 hours prior to admission (None/Any number)									
None	3	0.54	5.59	1	0.89	1.12	0.2	0.00	2.49
1-3 seizures	4	2.57	1.56	4	1.19	3.35	2.15	0.40	11.57
4-20 seizures	5	1.78	2.81	2	1.15	1.75	0.62	0.06	3.79
Quinine given prior to admission									
No	8	2.94	2.72	5	2.55	1.96	0.72	0.19	2.49
Yes	4	1.94	2.06	2	0.68	2.94	1.43	0.13	9.98
Previous medical admission to hospital									
No	11	4.44	2.48	6	3.15	1.91	0.77	0.23	2.27
Yes	1	0.44	2.25	1	0.09	11.69	5.20	0.07	408.44
Clinical examination on admission									
Case definition									
Definite	5	1.86	2.69	4	2.51	1.59	0.59	0.12	2.75
Probable	7	3.03	2.31	3	0.72	4.16	1.80	0.30	7.88

Table continued overleaf

* Cumulative duration between discharge and the first follow-up visit; The duration was variable for each patient.

Table 5.8 continued

Variable	Children			Adults			Incidence rate ratio (Adults / Children)	Lower 95% CI	Upper 95% CI
	No. of events	Discharge to 1st visit (person years)†	Incidence rate (per person-year)	No. of events	Discharge to 1st visit (person years)	Incidence rate (per person-year)			
Able to localise painful stimuli at Level 2									
No	7	2.79	2.50	6	3.12	1.92	0.76	0.21	2.66
Yes	5	2.09	2.39	1	0.10	9.67	4.11	0.09	36.74
Body temperature									
35.0-38.5 °C	7	3.01	2.33	3	1.40	2.14	0.92	0.15	4.04
38.6-39.4 °C	3	1.53	1.96	4	1.74	2.30	1.17	0.20	8.00
39.5-42.0 °C	2	0.34	5.82	0	0.09	NA	NA	NA	NA
Moderate – severe anaemia									
No	7	1.62	4.33	5	2.69	1.86	0.43	0.11	1.57
Yes	5	3.27	1.53	2	0.54	3.67	2.40	0.23	14.66
Clinical signs of jaundice									
No	11	4.40	2.50	7	3.15	2.23	0.89	0.29	2.51
Yes	1	0.49	2.05	0	0.00	NA	NA	NA	NA
Clinical signs of moderate – severe dehydration (No/Yes)									
No	11	4.86	2.26	7	3.23	2.17	0.96	0.31	2.70
Yes	1	0.02	44.33	0	0.00	NA	NA	NA	NA
Presence of extra heart sounds									
None	8	3.43	2.33	7	3.04	2.30	0.99	0.30	3.12
Yes	2	0.95	2.11	0	0.20	NA	NA	NA	NA
Missing info	2	0.51	3.93	0	0.00	NA	NA	NA	NA

Table continued overleaf

† Total of cumulative durations between discharge and the first follow-up visit for all patients; The duration was variable for each patient.

Table 5.8 continued

Variable	Children			Adults			Incidence rate ratio (Adults / Children)	Lower 95% CI	Upper 95% CI
	No. of events	Discharge to 1st visit (person years)‡	Incidence rate (per person-year)	No. of events	Discharge to 1st visit (person years)	Incidence rate (per person-year)			
Possibility of shock									
Unlikely	10	4.50	2.22	7	3.23	2.17	0.97	0.31	2.83
Likely	2	0.38	5.25	0	0.00	NA	0	0	0
Pulse pressure									
20-39 mmHg	1	0.82	1.22	1	1.01	0.99	0.81	0.01	63.61
40-79 mmHg	0	0.23	NA	3	1.86	1.61	NA	NA	NA
Missing info	11	3.83	2.87	3	0.35	8.46	2.95	5.3	11.15
Respiratory abnormality									
No	6	2.36	2.54	7	3.07	2.28	0.90	0.26	3.23
Yes	6	2.52	2.38	0	0.17	NA	NA	NA	NA
Possibility of respiratory distress									
Unlikely	12	4.53	2.65	7	3.23	2.17	0.82	0.27	2.25
Likely	0	0.35	NA	0	0.00	NA	NA	NA	NA
Presence of Organomegaly									
No	8	3.31	2.42	3	0.88	3.40	1.41	0.24	5.88
Yes	4	1.57	2.54	4	2.35	1.70	0.67	0.12	3.59
Enlarged spleen									
No	10	4.26	2.35	6	2.55	2.36	1.00	0.30	3.05
Yes	2	0.62	3.21	1	0.69	1.46	0.45	0.01	8.68
Enlarged liver (No/Yes)									
No	10	4.06	2.46	6	2.26	2.65	1.08	0.32	3.28
Yes	2	0.82	2.44	1	0.97	1.03	0.42	0.01	8.09

Table continued overleaf

‡ Total of cumulative durations between discharge and the first follow-up visit for all patients; The duration was variable for each patient.

Table 5.8 continued

Variable	Children			Adults			Incidence rate ratio (Adults / Children)	Lower 95% CI	Upper 95% CI
	No. of events	Discharge to 1st visit (person years)[§]	Incidence rate (per person-year)	No. of events	Discharge to 1st visit (person years)	Incidence rate (per person-year)			
In-hospital non-laboratory information									
Had witnessed seizures									
No	8	2.57	3.11	5	1.77	2.82	0.91	0.23	3.16
Yes	4	2.31	1.73	2	1.47	1.36	0.79	0.07	5.50
Number of witnessed seizures (1st episode)									
None	8	2.57	3.11	5	1.77	2.83	0.91	0.23	3.16
1-3 seizures	2	1.15	1.74	2	0.90	2.21	1.27	0.09	17.57
4-20 seizures	2	1.16	1.73	0	0.56	NA	NA	NA	NA
Seizure stoppage time									
1-2 days	2	2.00	1.00	1	1.02	0.98	0.98	0.02	18.82
3-48 days	2	0.31	6.43	1	0.44	2.24	0.35	0.01	6.70
No seizures recorded	8	2.57	3.11	5	1.77	2.82	0.91	0.23	3.16
Total seizure stoppage time									
1-2 days	5	2.91	1.72	4	1.37	2.92	1.70	0.34	7.90
3-48 days	5	1.47	3.40	2	1.17	1.70	0.50	0.05	3.06
No seizures recorded	2	0.50	3.99	1	0.69	1.46	0.36	0.01	7.00
Duration of unrousable coma									
Not in unrousable coma on admission	5	2.26	2.22	0	0.10	NA	NA	NA	NA
For less than 48 hours	3	1.64	1.83	3	1.47	2.04	1.12	0.15	8.36
For 48 hours or more	3	0.80	3.75	4	1.67	2.40	0.64	0.11	4.36
Missing info	1	0.18	5.41	0	0.00	NA	NA	NA	NA

Table continued overleaf

[§] Total of cumulative durations between discharge and the first follow-up visit for all patients; The duration was variable for each patient.

Table 5.8 continued

Variable	Children			Adults			Incidence rate ratio (Adults / Children)	Lower 95% CI	Upper 95% CI
	No. of events	Discharge to 1st visit (person years)**	Incidence rate (per person-year)	No. of events	Discharge to 1st visit (person years)	Incidence rate (per person-year)			
Coma recovery time									
1-2 days	2	1.32	1.51	1	0.70	1.42	0.94	0.02	18.06
3-4 days	5	2.21	2.26	4	2.03	1.97	0.87	0.17	4.04
5 and above	2	0.50	4.04	2	0.50	4.02	0.99	0.07	13.72
Missing Info	3	0.86	3.50	0	0.00	NA	NA	NA	NA
Total coma recovery time									
1-2 days	4	1.85	2.16	0	0.60	NA	NA	NA	NA
3-4 days	3	1.73	1.73	4	1.79	2.23	1.29	0.22	8.78
5 and above	5	1.22	4.11	3	0.84	3.58	0.87	0.14	4.47
Missing info	0	0.09	NA	0	0.00	NA	NA	NA	NA
Fever clearance time									
1 day	2	1.29	1.55	3	0.99	3.02	1.95	0.22	23.38
2-3 days	4	2.34	1.71	4	2.24	1.79	1.04	0.19	5.60
4-9 days	6	1.17	5.14	0	0.00	NA	NA	NA	NA
Missing info	0	0.09	NA	0	0.00	NA	NA	NA	NA
Total fever clearance time									
1-4 days	4	2.03	1.97	3	0.36	8.45	4.28	0.63	25.33
5-6 days	1	1.04	0.96	3	2.24	1.34	1.39	0.11	73.14
7-15 days	7	1.82	3.85	1	0.64	1.56	0.41	0.01	3.16
Quinine loading dose prescribed on admission									
No	11	4.10	2.68	7	2.48	2.83	1.05	0.35	2.97
Yes	0	0.26	NA	0	0.00	NA	NA	NA	NA
Missing	1	0.53	1.89	0	0.76	NA	NA	NA	NA

Table continued overleaf

** Total of cumulative durations between discharge and the first follow-up visit for all patients; The duration was variable for each patient.

Table 5.8 continued

Variable	Children			Adults			Incidence rate ratio (Adults / Children)	Lower 95% CI	Upper 95% CI
	No. of events	Discharge to 1st visit (person years)††	Incidence rate (per person-year)	No. of events	Discharge to 1st visit (person years)	Incidence rate (per person-year)			
Dose of quinine given on Day 0									
3-8.9 mg/kg	4	0.95	4.19	1	0.59	1.71	0.41	0.01	4.11
9.0-10.9 mg/kg	1	0.22	4.54	1	0.09	11.69	2.58	0.03	202.57
11.0-20.9 mg/kg	2	1.46	1.37	1	1.01	0.99	0.72	0.01	13.81
Missing info	5	2.25	2.22	4	1.55	2.58	1.16	0.23	5.41
Duration of hospital stay									
Less than 6 days	0	0.17	NA	0	0.00	NA	NA	NA	NA
6 to 8 days	7	3.41	2.05	6	3.06	1.96	0.96	0.27	3.32
More than 8 days	5	1.31	3.83	1	0.08	11.72	3.07	0.06	27.40
Laboratory based information									
Hypoglycaemia present on admission									
No	11	4.72	2.33	7	3.23	2.17	0.93	0.31	2.62
Yes	1	0.17	6.03	0	0.00	NA	NA	NA	NA
Random blood glucose on admission									
Less than 5 mmol/L	5	1.48	3.38	1	0.41	2.42	0.72	0.02	6.41
5 – 6.9 mmol/L	3	0.75	4.02	4	1.69	2.37	0.59	0.10	4.02
7 – 14.9 mmol/L	2	1.22	1.63	1	0.69	1.45	0.89	0.02	17.10
Missing info	2	1.44	1.39	1	0.45	2.25	1.61	0.03	30.93
Parasite count									
50,000 parasites/μL and below	8	2.44	3.28	4	1.70	2.36	0.72	0.16	2.68
> 50,000 parasites/μL	3	2.05	1.46	2	1.36	1.47	1.00	0.08	8.76
Missing info	1	0.39	2.54	1	0.17	5.76	2.27	0.03	178.17

Table continued overleaf

†† Total of cumulative durations between discharge and the first follow-up visit for all patients; The duration was variable for each patient.

Table 5.8 continued

Variable	Children			Adults			Incidence rate ratio (Adults / Children)	Lower 95% CI	Upper 95% CI
	No. of events	Discharge to 1st visit (person years)[‡‡]	Incidence rate (per person-year)	No. of events	Discharge to 1st visit (person years)	Incidence rate (per person-year)			
Parasite clearance time									
1 day	4	0.80	4.96	1	1.53	0.66	0.13	0.00	1.33
2 days	5	2.62	1.91	3	1.44	2.08	1.09	0.17	5.60
3-4 days	2	1.08	1.85	1	0.09	11.70	6.34	0.11	121.76
Missing info	1	0.37	2.63	2	0.18	11.17	4.25	0.22	250.51
Haemoglobin concentration									
3.0-9.9 g/dL	4	2.63	1.53	2	0.54	3.67	2.41	0.22	16.83
10.0-15.0 g/dL	6	1.48	4.05	1	0.77	1.31	0.32	0.01	2.66
Missing info	2	0.78	2.57	4	1.92	2.08	0.81	0.12	8.92
HIV infection									
No	3	1.03	2.91	0	0.00	NA	NA	NA	NA
Yes	0	0.10	NA	1	0.45	2.24	NA	NA	NA
Missing	9	3.75	2.40	6	2.79	2.15	0.90	0.26	2.82
Serum Sodium concentration									
<135 mmol/L	5	1.18	4.24	2	0.62	3.22	0.76	0.07	4.63
135-146 mmol/L	2	1.67	1.19	0	0.09	NA	NA	NA	NA
>146 mmol/L	0	0.29	NA	0	0.00	NA	NA	NA	NA
Missing info	5	1.75	2.86	5	2.52	1.98	0.69	0.16	3.01
Serum Calcium concentration									
<2 mmol/L	2	0.93	2.15	1	0.50	2.00	0.93	0.02	17.84
2-3 mmol/L	0	0.09	NA	0	0.00	NA	NA	NA	NA
>3 mmol/L	3	1.18	2.54	4	1.13	3.52	1.39	0.23	9.46
Missing info	7	2.69	2.61	2	1.60	1.25	0.48	0.05	2.52

Table continued overleaf

[‡‡] Total of cumulative durations between discharge and the first follow-up visit for all patients; The duration was variable for each patient.

Table 5.8 continued

Variable	Children			Adults			Incidence rate ratio (Adults / Children)	Lower 95% CI	Upper 95% CI
	No. of events	Discharge to 1st visit (person years)[ff]	Incidence rate (per person-year)	No. of events	Discharge to 1st visit (person years)	Incidence rate (per person-year)			
Serum Chloride concentration									
<95 mmol/L	1	0.27	3.71	0	0.00	NA	NA	NA	NA
95-105 mmol/L	2	0.44	4.57	1	0.61	1.65	0.36	0.01	6.92
>105 mmol/L	2	1.32	1.32	3	1.02	2.93	1.93	0.22	23.12
Missing info	7	2.86	2.86	3	1.60	1.87	0.76	0.13	3.35
White blood cell count									
2000-4700 cells/L	3	1.08	2.79	4	1.36	2.95	1.06	0.18	7.22
4701-6700 cells/L	4	1.44	2.78	0	1.26	NA	NA	NA	NA
6701-27000 cells/L	4	1.96	2.04	0	0.36	NA	NA	NA	NA
Missing info	1	0.41	2.95	3	0.26	11.73	4.84	0.39	254.02
At discharge									
Has early-onset neurological deficits									
No	7	3.73	1.88	5	2.99	1.67	0.89	0.22	3.26
Yes	5	1.16	4.32	2	0.25	8.07	1.87	0.18	11.43

[ff] Total of cumulative durations between discharge and the first follow-up visit for all patients; The duration was variable for each patient.

The rate of deficits in children with hyperthermia was 5.82 deficits per person-year. The rate decreased with increasing categories of body temperature in both children and adults. Older cases with signs of moderate to severe anaemia had just over 2 times the rate of sequelae than younger cases. Children who had clinical features suggestive of shock had a higher frequency of deficits than those who did not have features suggestive of shock. Cases who did not have a palpable or enlarged spleen had similar rates of deficits between children and adults. Adults with enlarged spleens had a lower rate of deficits than children (IRR=0.45 [95% CI 0.01-8.68]).

Witnessed seizures in hospital were associated with a reduced frequency of sequelae during follow-up in both children and adults. However longer seizure stoppage times were associated with increased incidence rates of sequelae. Child cases who were unconscious for 48 hours and more had an incidence rate of 3.75 deficits per person-year which was higher than the rate in adult cases, 2.40 deficits per person-year. As the coma recovery time increased, so did the rate of sequelae in both groups. A total fever clearance time of 1 to 4 days resulted in a four-fold rate of late-onset deficits in adults compared with children. Longer durations were associated with a smaller ratio. Children who were given the lower dose of quinine on Day 0 had a higher incidence compared to adults. The opposite was found in cases given the standard dose of quinine. Adults had twice the rate of deficits. The higher doses of quinine were associated with smaller rates within both groups and fairly similar rates between groups. Those cases who stayed for more than 8 days in hospital had the higher rates of deficits than those who spent shorter durations. Adults who spent more than 8 days were more likely to develop late-onset deficits compared to children.

Blood glucose concentrations between 7 and 14 mmol/L were associated with a lesser frequency of deficits in both children and adults. A shorter duration of parasite clearance time was associated with a greater risk of deficits in children. The reverse was found in adults, who had more deficits with increasing clearance times. As a consequence, the incidence rate ratio between children and adults was 6.34 if the parasite clearance time was 3 to 4 days, the maximum period it took to clear parasites in the study. Adult cases who had sequelae at discharge had an incidence

rate of late-onset deficits that was almost twice the rate in children who were discharged with early-onset sequelae.

5.3.2 Crude and adjusted relative risk estimates for late-onset neurological sequelae.

Time-to-event analysis using regression on the Weibull distribution was employed to determine the association between explanatory variables and late-onset deficits. This distribution was considered more appropriate than an exponential or constant hazard to model the data because it did not assume that the risk for the event, in this case the detection of late-onset deficits, was constant during the follow-up period. It appeared from the data and the literature that the risk for late-onset deficits was likely to decline with increasing time after cerebral malaria. Crude and adjusted hazard ratios (adjusted for case definition, centre or age) are given in Table 5.9. Centre was highly associated with outcome. Kapchorwa survivors, who were in general older, had a reduced risk for deficits compared to those from Mbale. This association was not modified by adjusting for case definition, or age. Adult survivors had a hazard ratio of 0.76 compared to children although this was not significant at the 5% level. The risk declined with age when it was categorised into three groups. The lower group was not used as the referent one because none of the younger children had late-onset deficits. The decline was modified when centre was adjusted for as shown.

The number of reported seizures in the 24 hours before admission did not seem to be independently associated with deficits. A previous history of admission though not highly associated with outcome, had a 2 fold effect on the risk estimate. The depth of coma when expressed as the inability to localise a painful stimulus was not associated with any increase in the hazard ratio, crude or adjusted. However, when coma was expressed in terms of coma scores, survivors who had lower scores were more likely to have late-onset deficits compared to those who were less comatose. Hyperthermia resulted in a hazard ratio of about 3 when compared with temperatures below 38.5 ^{o}C. This clinically important effect was not modified by case definition, centre or age and was not statistically significant at the 5% level.

Table 5.9: Crude and adjusted hazard ratios for late-onset neurological sequelae among survivors of cerebral malaria who attended a follow-up visit (n=52)

Risk factor			Variable adjusted for					
			Case definition		Centre		Age group	
	Crude HR	P value	HR	*95% CI*	HR	*95% CI*	HR	*95% CI*
Factors shown to have differences in the descriptive analyses								
Centre								
Mbale	1		1		NA*	-	1	
Kapchorwa	0.30	**0.04**	0.30	*0.09-0.95*	-	-	0.27	*0.07-1.01*
Age group 1								
≤ 10 yrs	1		1		1		NA	-
> 10 years	0.76	0.56	0.80	*0.26-2.43*	1.17	*0.39-3.50*	-	-
Age group 2								
1-4 yrs	1.31	0.66	1.37	*0.38-4.88*	0.61	*0.16-2.26*	NA	-
5-9 yrs	1		1		1		-	-
10 yrs and above	0.82	0.71	0.91	*0.26-3.13*	1.05	*0.35-3.14*	NA	-
Number of seizures within 24 hours prior to admission								
None	1		1		1		1	
1-3 seizures	0.77	0.67	0.67	*0.19-2.41*	0.83	*0.25-2.76*	0.68	*0.19-2.38*
4-20 seizures	0.85	0.79	0.79	*0.23-2.76*	0.74	*0.22-2.54*	0.76	*0.22-2.70*
Admitted to hospital before	2.05	0.35	1.99	*0.44-8.97*	1.21	*0.25-5.76*	1.94	*0.43-8.82*
Unable to localise painful stimuli	1.18	0.73	1.03	*0.29-3.67*	1.08	*0.40-2.89*	1.02	*0.32-3.21*

Table continued overleaf

* Not applicable

Table 5.9 continued

Risk factor			Variable adjusted for					
			Case definition		Centre		Age group	
	Crude HR	P value	HR	95% CI	HR	95% CI	HR	95% CI
Blantyre Coma Score†								
0-2	1.10	0.93	1.38	0.11-17.69	1.32	0.12-14.77	1.11	0.10-12.32
3-5	1		1		1		1	
Missing info	1.39	0.75	1.57	0.19-12.79	3.77	0.45-31.40	1.65	0.20-13.25
Glasgow Coma Score‡								
3-8	1.62	0.38	2.14	0.61-7.49	0.78	0.16-3.67	1.78	0.57-5.54
9-12	1		1		1		1	
Missing info	1.71	0.41	1.85	0.51-6.67	0.46	0.07-3.25	1.52	0.41-5.73
Body temperature								
35.0-38.5 °C	1		1		1		1	
38.6-39.4 °C	0.85	0.74	1.02	0.34-3.09	0.98	0.36-2.64	0.90	0.33-2.44
39.5-42.0 °C	2.68	0.22	3.48	0.59-20.39	2.36	0.49-11.37	2.66	0.55-12.93
Presence of moderate to severe anaemia	0.72	0.50	0.67	0.25-1.76	0.49	0.18-1.34	0.55	0.19-1.57
Presence of jaundice	0.92	0.93	0.92	0.12-7.22	0.60	0.07-4.76	0.88	0.11-6.95
Presence of any respiratory abnormality	1.09	0.86	1.05	0.38-2.89	0.65	0.22-1.95	0.94	0.31-2.85
Presence of any extra heart sounds								
No	1		1		1		1	
Yes	0.76	0.71	0.73	0.16-3.23	0.66	0.15-2.90	0.70	0.15-3.15
Missing info	2.14	0.32	2.03	0.43-9.56	1.33	0.28-6.40	1.93	0.40-9.28
Presence of organomegaly	0.70	0.45	0.73	0.26-2.04	0.82	0.32-2.11	0.75	0.27-2.06
Presence of enlarged spleen	0.99	0.99	1.08	0.30-3.92	0.90	0.26-3.11	1.06	0.30-3.74

Table continued overleaf

† Children aged 5 years and below
‡ Children aged over 5 years

Table 5.9 continued

Risk factor	Crude HR	P value	Variable adjusted for: Case definition HR	Case definition 95% CI	Centre HR	Centre 95% CI	Age group HR	Age group 95% CI
Pulse pressure								
20-39 mmHg	0.67	0.66	0.67	*0.11-4.01*	0.65	*0.11-3.89*	0.88	*0.15-5.35*
40-79 mmHg	1		1		1		1	
Missing info	3.00	0.09	3.33	*0.85-12.98*	2.30	*0.55-9.63*	8.40	*1.49-47.28*
Had witnessed seizures	0.55	0.23	0.56	*0.21-1.46*	0.52	*0.20-1.37*	0.56	*0.21-1.47*
Number of witnessed seizures on first episode								
None	1		1		1		1	
1-3 seizures	0.74	0.60	0.75	*0.24-2.35*	0.62	*0.20-1.98*	0.77	*0.24-2.44*
4-20 seizures	0.37	0.19	0.37	*0.08-1.64*	0.39	*0.09-1.75*	0.36	*0.08-1.62*
Fever clearance time								
1 day	1		1		1		1	
2-3 days	0.75	0.61	0.75	*0.25-2.30*	0.81	*0.26-2.53*	0.74	*0.24-2.28*
4-9 days	3.27	0.06	3.23	*0.90-11.58*	2.35	*0.57-9.69*	3.45	*0.89-13.31*
Total fever clearance time								
1-4 days	1		1		1		1	
5-6 days	0.40	0.13	0.25	*0.06-1.08*	0.43	*0.13-1.49*	0.34	*0.08-1.39*
7-15 days	1.13	0.81	1.16	*0.42-3.19*	1.04	*0.37-2.88*	1.07	*0.38-3.04*
Has hypoglycaemia	3.55	0.23	3.54	*0.45-28.13*	3.25	*0.41-25.53*	3.31	*0.41-26.65*
Random blood glucose								
< 5 mmol/L	1.13	0.82	1.08	*0.36-3.27*	1.11	*0.37-3.29*	0.89	*0.26-3.02*
5-6.9 mmol/L	1		1		1		1	
≥7 mmol/L	0.52	0.35	0.52	*0.13-2.01*	0.48	*0.12-1.86*	0.44	*0.11-1.82*
Missing info	0.61	0.47	0.58	*0.15-2.30*	0.48	*0.12-1.92*	0.48	*0.11-2.08*
Haemoglobin concentration								
3.0-9.9 g/dL	0.63	0.40	0.61	*0.20-1.83*	0.55	*0.18-1.65*	0.58	*0.19-1.77*
10.0-15.0 g/dL	1		1		1		1	
Missing info	0.67	0.47	0.69	*0.23-2.08*	0.60	*0.20-1.80*	0.77	*0.24-2.48*

Table continued overleaf

Table 5.9 continued

Risk factor			Variable adjusted for					
			Case definition		Centre		Age group	
	Crude HR	P value	HR	*95% CI*	HR	*95% CI*	HR	*95% CI*
White blood cell count								
2,000-4,700	1.77	0.36	1.65	*0.47-5.82*	2.38	*0.66-8.63*	1.74	*0.50-6.00*
4,701-6,700	1		1		1		1	
6,701-27,000	1.20	0.79	1.09	*0.26-4.56*	1.49	*0.36-6.10*	1.01	*0.23-4.31*
Missing info	6.11	**0.02**	6.02	*1.36-26.64*	4.45	*1.01-19.67*	5.81	*1.32-25.63*
Other explanatory factors								
Quinine given prior to admission	1.03	0.94	1.00	*0.37-2.67*	0.95	*0.36-2.53*	0.97	*0.36-2.63*
Presence of moderate to severe dehydration	44.72	**0.001**	50.74	*4.97-517.91*	44.73	*4.45-449.30*	43.15	*4.40-423.04*
Likely to be in shock	2.54	0.21	2.43	*0.51-11.57*	1.26	*0.25-6.36*	2.36	*0.52-10.79*
Duration taken to localise pain								
Localises pain on admission	1		1		1		1	
≤ 48 hours	0.94	0.91	1.21	*0.27-5.41*	1.04	*0.31-3.44*	1.22	*0.34-4.45*
> 48 hours	1.36	0.59	1.70	*0.43-6.70*	1.54	*0.48-4.93*	2.06	*0.50-8.49*
Missing info	3.34	0.28	3.30	*0.37-29.69*	3.27	*0.37-29.23*	3.62	*0.40-33.11*
Coma recovery time								
1-2 days	1		1		1		1	
3-4 days	1.29	0.70	1.25	*0.33-4.73*	1.67	*0.44-6.38*	1.29	*0.35-4.86*
5 and above	2.78	0.18	2.84	*0.63-12.74*	3.37	*0.74-15.31*	2.91	*0.64-13.12*
Missing Info	2.21	0.33	1.97	*0.36-10.64*	2.71	*0.54-13.61*	1.95	*0.37-10.30*
Total coma recovery time								
1-2 days	1		1		1		1	
3-4 days	1.08	0.91	1.05	*0.30-3.65*	1.47	*0.40-5.41*	1.13	*0.33-3.94*
5 and above	2.94	0.08	3.18	*0.92-11.05*	2.90	*0.85-9.81*	3.20	*0.92-11.14*
Seizure stoppage time								
1-2 days	1		1		1		1	
3-48 days	3.91	0.09	3.80	*0.75-19.15*	4.03	*0.81-19.97*	4.43	*0.87-22.63*
No recorded seizures	2.88	0.10	2.86	*0.81-10.08*	3.10	*0.88-10.93*	2.93	*0.83-10.32*

Table continued overleaf

Table 5.9 continued

Risk factor	Crude HR	P value	Variable adjusted for: Case definition HR	Case definition 95% CI	Centre HR	Centre 95% CI	Age group HR	Age group 95% CI
Total seizure stoppage time								
1-2 days	1		1		1		1	
3-48 days	1.22	0.69	1.21	*0.45-3.25*	1.25	*0.46-3.37*	1.28	*0.47-3.47*
No recorded seizures	1.15	0.83	1.19	*0.32-4.42*	1.17	*0.32-4.35*	1.28	*0.33-4.90*
Dose of quinine given on Day 0								
3-8.9 mg/kg	2.56	0.27	2.94	*0.52-16.54*	2.55	*0.48-13.60*	2.49	*0.47-13.25*
9.0-10.9 mg/kg	1		1		1		1	
11.0-20.9 mg/kg	0.31	0.11	0.31	*0.07-1.34*	0.37	*0.09-1.58*	0.31	*0.07-1.32*
Missing info	0.61	0.39	0.55	*0.17-1.76*	0.80	*0.25-2.54*	0.60	*0.19-1.85*
Parasite count								
≤ 50,000 parasites/μL	1		1		1		1	
> 50,000 parasites/μL	0.47	0.15	0.46	*0.16-1.32*	0.59	*0.19-1.79*	0.45	*0.16-1.30*
Missing info	1.60	0.55	1.50	*0.31-7.31*	1.12	*0.23-5.42*	1.58	*0.33-7.46*
Parasite clearance time								
1 day	1		1		1		1	
2 days	0.92	0.88	0.87	*0.25-3.05*	0.94	*0.31-2.89*	0.83	*0.25-2.73*
3-4 days	1.25	0.76	1.16	*0.23-5.69*	1.33	*0.32-5.59*	1.02	*0.21-5.08*
Missing info	3.59	0.10	3.32	*0.62-17.89*	2.51	*0.54-11.73*	3.25	*0.68-15.48*
HIV infection								
No	1		1		1		1	
Yes	0.46	0.51	0.40	0.04-4.24	0 90	*0.08-9.69*	0.53	*0.05-6.11*
Missing	0.62	0.47	0.62	0.17-2.29	1.14	*0.29-4.49*	0.66	*0.17-2.56*

Table continued overleaf

Table 5.9 continued

Risk factor			Variable adjusted for					
			Case definition		Centre		Age group	
	Crude HR	P value	HR	*95% CI*	HR	*95% CI*	HR	*95% CI*
Serum Sodium concentration								
<135 mmol/L	3.55	0.11	3.54	*0.73-17.08*	3.22	*0.67-15.56*	4.22	*0.85-21.04*
135-146 mmol/L	1		1		1		1	
Missing info	1.77	0.46	1.85	*0.38-8.94*	2.73	*0.54-13.78*	2.23	*0.45-10.92*
Serum Calcium concentration								
<2 mmol/L	1		1		1		1	
>3 mmol/L	1.35	0.66	1.28	*0.32-5.06*	1.22	*0.31-4.73*	1.41	*0.36-5.51*
Missing info	0.83	0.78	0.75	*0.19-3.03*	0.92	*0.24-3.59*	0.77	*0.19-3.04*
Serum Chloride concentration								
<95 mmol/L	1.63	0.67	1.43	*0.14-14.87*	1.76	*0.18-17.34*	1.38	*0.13-14.34*
95-105 mmol/L	1		1		1		1	
>105 mmol/L	0.78	0.73	0.75	*0.18-3.17*	0.65	*0.15-2.76*	0.76	*0.18-3.18*
Missing info	0.71	0.61	0.65	*0.17-2.50*	0.78	*0.21-2.89*	0.64	*0.17-2.47*
Had early-onset neurological deficits	3.00	**0.02**	2.99	*1.14-7.86*	3.21	*1.26-8.22*	3.03	*1.11-8.22*

Survivors who had tonic-clonic seizures in hospital were about 50% less likely to have late deficits than those who did not. A step wise decline in the hazard with increasing number of seizures was seen. A duration of over 3 days for fevers to clear was strongly associated with a greater risk of deficits by about 3 times (P = 0.07). This effect reduced in magnitude when the number of days for which patients were reportedly febrile were added, i.e. total fever clearance time. Hypoglycaemia was associated with a greater risk of deficits at the 23% level. The three-fold increase in risk persisted when case definition, centre and age were controlled for separately.

One survivor who was admitted with features of moderate to severe dehydration had a late-onset neurological deficit. As a result the hazard ratio was very large, 44.72 (P = 0.001). The adjusted estimates had very wide confidence intervals because comparison was made with a group in which there was no survivor with deficits, i.e. dehydrated and no late-onset deficits. Likewise, two survivors who had features of shock on admission, developed late-onset deficits. The comparison cell of shock and no deficits had no survivor that attended follow-up. Survivors who had been in coma for 5 or more days had a greater risk of deficits than those who had been in coma for 1 to 2 days. This effect was similar but of less magnitude if those who had been in coma for 3 to 4 days were compared with the same referent group. The total coma recovery time showed a similar effect. The seizure stoppage time was a risk factor for deficits. The total seizure stoppage time showed a similar association though the study was not able to show if they were real or could have occurred by chance.

The risk estimate for deficits among cases that were given the higher dose of quinine was compared with the standard dose of 10mg/kg. The crude hazard ratio was 0.31 and did not change after adjusting for the other factors separately. Patients who received the lower dose had a greater potential for deficits compared to those who received the standard dose. The finding of deficits at discharge was associated with a three-fold risk of late-onset deficits (P = 0.02).

5.3.3 Risk factors determined by multivariable survival analysis

A model to determine the risk factors that are associated with late-onset deficits was constructed in a step-wise manner. The first variable inserted into the model was age, because *a priori* the hypothesis was that it influenced the risk for sequelae. Next centre was added, because it was an important confounding factor and adjusting for it allowed other unmeasured factors that are related to study site to be taken into account. These were followed by factors that were shown to be associated with the outcome up to the 15% alpha level. They remained in the model if their P value for the LR test was significant up to the 5% level or they were considered to be clinically significant. The next variables that were added to the model are those which have already been described in the literature as risk factors and listed in the plan of analysis at the onset. Likewise they remained in the model if they met the requirements above. Lastly, clinically relevant factors were added into the model if they had not already been selected by any of the above procedures. These were left in the model. Care was taken not to leave too many variables in the model since the number of events was small. In this way the models based on the Weibull distribution and shown in Table 5.10 were developed. Comparison models using Cox regression are given in Table D in Appendix V.

Model 1 in Table 5.10 shows two models. The difference between Model 1 and 2 is that the latter does not include clinically significant variables. The results of both are fairly similar however, some values of the hazard ratios differ and the width of the confidence intervals are narrower in Model 2. Survival analysis takes the time to event into account. It is important for me to mention at this stage that in reality the time period that forms the analysis time is better described as the time to detection of the deficit and not purely the time to the manifestation of deficits. Patients who had deficits at discharge were not excluded from the denominator because a variable that had information on the presence or absence of early onset deficits was included into the model. This was done because it was of clinical value to the health practitioners to use that information to be able to predict the likelihood of late-onset deficits.

Table 5.10: Risk factors for late-onset neurological sequelae by multivariable survival analysis using the Weibull distribution

Risk factor	Hazard Ratio*	Lower 95% CI	Upper 95% CI	LR test
Model 1 (n=90)†				
Aged over ten years	1.84	0.51	6.67	0.34
Admitted to hospital before	0.69 (C‡)	0.54	38.62	0.68
Body temperature	(C)			0.56
35.0-38.5 °C	1			
38.6-39.4 °C	1.47	0.45	4.82	
39.5-42.0 °C	3.19	0.39	26.11	
Fever clearance time				0.08
1 day	1			
2-3 days	0.87	0.22	3.36	
4-9 days	7.52	1.11	50.69	
Seizure stoppage time				0.06
1-2 days	1			
3-48 days	4.56	0.54	38.62	
No seizures recorded	7.92	1.09	57.40	
Total coma recovery time	(C)			0.67
1-2 days	1			
3-4 days	2.72	0.48	15.37	
5 and above	1.39	0.28	6.95	
Was hypoglycaemic on admission	1.91 (C)	0.10	37.75	0.67
Had deficits at discharge	5.01	1.26	19.93	**0.02**
Model 2 (n=90)§				
Aged over ten years	1.64	0.51	5.28	0.40
Fever clearance time				0.09
1 day	1			
2-3 days	0.71	0.19	2.64	
4-9 days	4.62	0.79	26.95	
Seizure stoppage time				**0.04**
1-2 days	1			
3-48 days	4.80	0.82	27.97	
Missing	4.95	1.13	21.78	
Had deficits at discharge	8.07	2.14	30.47	**0.002**

* Derived from a Weibull model and includes clinically significant variables
† Adjusted for centre and using age as two categories
‡ 'C' refers to clinically significant factors which were included in the model without being statistically significant.
§ Derived from a Weibull model and does not include clinically significant variables as in Model 1.

In Model 1, the duration taken for seizures to cease was independently associated with the detection of late-onset seizures. The hazard ratio increased with longer seizure stoppage time. The presence of deficits at discharge, i.e. early-onset deficits was also highly associated with late-onset deficits with a hazard ratio of about 5. Fever of durations over 3 days increased the risk of deficits by 7 fold. The risk of late-onset deficits in survivors who had been admitted to hospital before (a clinically relevant variable) was less than those who had not been admitted before. Hyperthermia and hypoglycaemia on admission were associated with HR of 3.19 (95% CI 0.39-26.11) and 1.91 (0.10-37.75) respectively though in both cases there was no statistical significance. Model 1 was repeated using age in three categories instead of two and the HRs were similar for all variables and as a result the findings are not summarised in the Table. To assess the fit of the Weibull model to the data, Cox-Snell residuals were used. A plot of the cumulative hazard H (obtained from the KM survival estimates) against the Cox-Snell residuals for Model 1 is given in Figure 5.2.

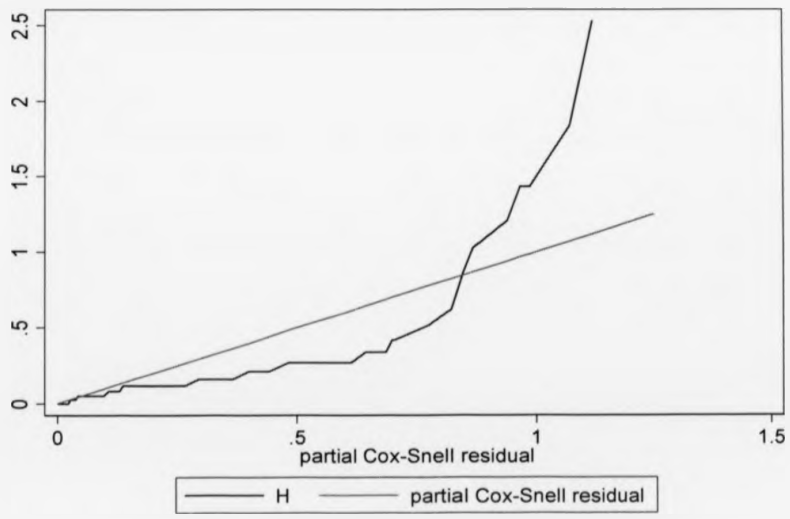


Figure 5.2: Cox-Snell residuals to evaluate the fit of the Weibull Model, Model 1 in Table 5.10

The residual analysis of the fit of the Model shows that the Weibull distribution did fit the data but it was not a perfect fit. The model was redone without the clinically significant variables to give Model 2. The same goodness of fit test was performed and given in Figure 5.3 below.

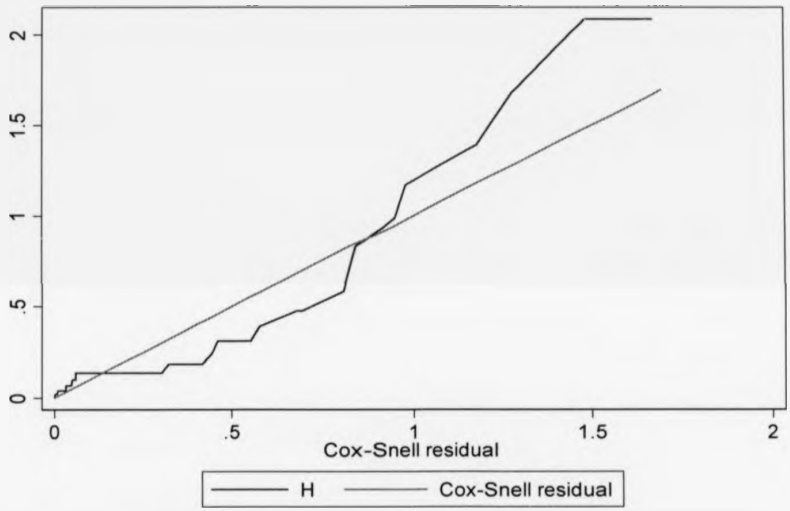


Figure 5.3: Cox-Snell residuals to evaluate the fit of the Weibull Model, Model 2 in Table 5.10

On inspection the graphs showed that Model 2 was a better fit of the data than Model 1 in Table 5.10. It was therefore more appropriate to use the findings of Model 2 rather than Model 1. A graph of the hazard function over analysis time for Model 2 showed that it increased rather than decreased, see Figure 5.4. This was in agreement with the shape parameter, p, which had a value of 1.78 (P = 0.001).

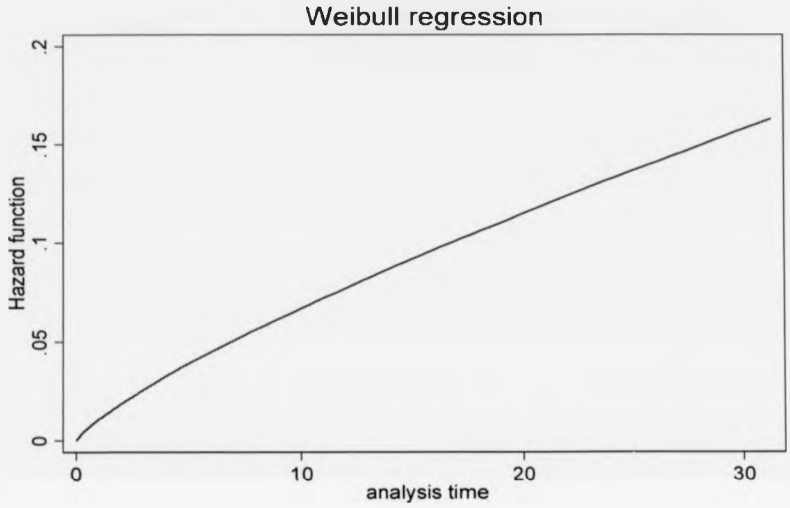


Figure 5.4: Graph of the hazard function of Model 2 in Table 5.10 over analysis time (in weeks).

The modelling process was repeated with Cox regression to see how this compared with the Weibull regression results. The findings Model 1b (corresponding to Model 1 of the Weibull model) and Model 2b (corresponding to Model 2 of the Weibull model) are given in Table D in the appendix. The HRs in Model 1b were different for some categories and the confidence intervals wider. However, the HRs of Models 2 and 2b were agreeable though those of the former were more precise because of their narrower 95% Confidence Intervals. The test of the proportional hazard assumption (based on Schoenfeld residuals) did not show any violation of the assumption in the global or detailed tests (except one category). However the assumption that the baseline hazard was constant over time was violated. The goodness-of-fit plot of Model 2b was less compatible with the data than Model 2. As such, the results of Model 2 were more suitable.

Chapter 6

6. DISCUSSION

6.1 Number of cerebral malaria cases enrolled during study period

The study set out to determine the natural history of neurological sequelae in children and adults in Uganda and elucidate any differences between the two groups. In order to do this, the number of patients needed to estimate effects with three-fold differences was calculated to be 364 patients (274 plus 90 patients to account for deaths and losses to follow-up). For this reason and others which have been mentioned in the methodology, a multi-centre study design was employed. Some benefits of using this approach will be highlighted later on. During fieldwork the study evolved to take into account some of the practical realities on the ground. One such reality was that far fewer than expected numbers of cerebral malaria cases occurred during the extended study period. A number of factors contributed to this situation. The study hospitals were selected from those with high "suitability scores" during the pre-study visit in July 2002 as shown in Table 3.2. One of the parameters included in the score was having more than 50 recorded cases of cerebral malaria per year. Mbale hospital (64 recorded cases of cerebral malaria out of 176 severe malaria admissions between January and December 1999) and Mutolere hospital (52 recorded cases out of 99 severe malaria admissions during the same period) met that requirement. The other two hospitals, Kabale hospital (10 recorded cerebral malaria cases out of 37 severe malaria admissions) and Kapchorwa hospital (no records on admissions that could be reviewed at that time) did not have records of sufficient numbers to receive a score on the scale. Anecdotal reports from the clinical and district health staff gave the indication that the frequency of cerebral malaria was higher than the records portrayed. Additionally both hospitals are prone to epidemics of malaria as has been documented by other researchers (Kiszewski and Teklehaimanot 2004). This potential that both hospitals had to contribute cases towards the study were taken into account, the more so since there was the possibility of epidemics in the area fuelled by the *El Niño* (ENSO) phenomenon during the study period.

Despite warnings by the government of the impending heavy rains in 2002 (see newspaper clips of these in Appendix VI) there was no epidemic of malaria at the

study sites that year or the next. In addition, the occurrence of cerebral malaria in all four sites was lower than anticipated. One reason for this appears to have been overdiagnosis of cerebral malaria in those hospitals in the pre-study period. Patients that had been admitted to hospital with fever and impaired consciousness with a provisional diagnosis of "cerebral malaria" sometimes did not meet any of the requirements for the *Eligibility checklist 1* and *2*. This was more pronounced in Kabale and Mutolere hospitals where at the onset of the study it was observed that some patients who had features suggestive of cerebral malaria did not have demonstrable falciparum parasitaemia. And yet, these cases recovered on quinine as the sole definitive treatment. In Kabale hospital at the time there was a cross-sectional study on severe malaria and they noticed the same phenomenon. To begin with, little attention was paid to this and it is only after the first rainy season that we began to wonder why there was this trend. We decided that suspected cases of cerebral malaria would have serial smears at least six hours apart to increase the chances of finding parasitaemia. At the same time, the procedures in the laboratory for detecting malaria parasites were reviewed to find out if there were any reasons for the negative slides. I also arranged an exercise in which I got the laboratory staff at both Mutolere and Kabale hospitals to examine five slides made at Mbale hospital. In all cases, they were able to detect the presence or absence of malaria parasites and identity them to species. Next we examined the laboratory records to determine the proportion of slides that were positive in the preceding months. I also retrieved the case records for patients admitted with the diagnosis "severe malaria" and "cerebral malaria" for the period 1991 and 2002 during which there was a reported epidemic of malaria in the region. Examination of the case records for cases with "cerebral malaria showed that less than 50% of them could meet the requirements for any definition of cerebral malaria. I have described the process taken to arrive at this conclusion in Appendix VI.

It began to be clear that cerebral malaria had been over diagnosed. For example, unconscious patients were not regularly being lumbar punctured. Sometimes this was because of the lack of lumbar puncture needles or sterile implements. The features of meningitis or encephalitis overlap with those of cerebral malaria and it is important to carry out a lumbar puncture to exclude them in a patient with non-traumatic coma. (Berkley, Mwangi *et al.* 1999). Blood glucose was not measured

routinely and it is possible that those patients who were unconscious because of a low blood sugar may have been misclassified as cerebral malaria. Some children who were unconscious after convulsions i.e. the post-ictal phase may have been recorded as cerebral malaria as well. In a retrospective review of the case records of 112 adults admitted to the Accident and Emergency Unit of Lagos University Hospital between January 1990 and June 1996, with a diagnosis of cerebral malaria, the authors found that 52 patients (46%) could fulfil the research definition for cerebral malaria. (Okubadejo and Danesi 2004). The likely diagnoses in those who were misdiagnosed include encephalitis (3 cases), meningitis (17 cases), septicaemia (23 cases), hypoglycaemia (6 cases), epilepsy (8 cases), chronic liver failure (2 cases) and subarachnoid haemorrhage (1 case). It is precisely because of these differential diagnoses that procedures were put in place at the onset of the Uganda study to exclude them.

The problem of case numbers was not restricted to this study. Around the same period there was study on cerebral malaria in an endemic area of Tanzania. Makani *et al.* (2003) studied adult patients admitted with altered mentation to Muhimbili National hospital in Dar-es-Salaam, Tanzania from October 2000 to July 2001. One hundred and ninety-nine patients were admitted with a provisional diagnosis of cerebral malaria (mean age at admission was 34.5 years, 95% CI 23.6-36.4). Only 15 patients (7.5%) had detectable parasitaemia and only 2 patients (1%) met the WHO research definition for cerebral malaria. The authors suggest that the huge difference between the presumptive diagnosis and microscopy-based diagnosis may be because a) prior treatment with antimalarials may have reduced parasite densities without modifying the course of the disease, or b) that some slide-negative patients did actually have cerebral malaria ("slide-negative" cerebral malaria). This could have been the case in this study as well. In early 1999, an epidemic of cerebral malaria occurred in the south western areas of Uganda. Health centres and hospitals were overflowing with patients. Many of the sick died. In the months after that the health authorities sent out district education teams to educate people about malaria. Some vector control measures were put in place before the rainy seasons e.g. indoor spraying in schools. Antimalarials were distributed to health centres. In this way the population may have become sensitized of the need to beware of 'fever'. As a result their health seeking behaviour may have changed making them seek treatment

earlier than was the case before. At the same time, the health personnel appear to have become more aggressive in their antimalarial prescribing habits. Widespread use of antimalarials may have prevented a proportion of people from developing severe disease and or modified the extent of parasitaemia without affecting the course of disease as described above. In this series, 83 cases reported use of an antimalarial in the month preceding admission, of which 50 cases were said to have used only chloroquine. If this trend of antimalarial use was the same in Kabale and Kisoro districts which have malaria transmission intensities that are similar to Kapchorwa, then antimalarial use cannot be modifying the course of progression to cerebral malaria in ill patients in the south-western part of the country and not in the eastern parts unless parasite resistance differs considerably or the strains of the parasite.

Antimalarial use in inadequate doses or via chloroquine resistance may be affecting the degree of parasitaemia by decreasing it without halting progress of disease. Sowunmi (1994) on the other hand suggests that chloroquine resistance of the malaria parasite due to the increased use of chloroquine could be one of the reasons for the apparent increase in the number of adults with cerebral malaria in Ibadan, a malaria endemic area. Clearly this was not the case in this study though the findings in Ibadan cannot be extrapolated to the study sites because of the different levels of malaria transmission. In these highland areas in which malaria parasitaemias may not reach the levels of endemic areas could widespread antimalarial use be causing 'slide-negative' cerebral malaria as suggested in the Tanzanian study or could sequestration of parasites be more pronounced? A historical event may be of relevance here. Between 1959 and 1963, the Kigezi* Malaria Eradication Project was implemented (Zulueta, Kafuko *et al.* 1961; Zulueta, Kafuko *et al.* 1964). By using a combination of insecticidal spraying of houses and mass distribution of chloroquine-pyrimethamine, malaria was eradicated from the region. However, at the end of the project imported cases of malaria were causing localised outbreaks. This past experience may be having current implications.

'Aparasitaemic' cerebral malaria is rare. Walker and Salako reported 5 children with cerebral malaria who were admitted with negative slides for *P. falciparum* (Walker,

* Consisted of the current districts in the south western part of Uganda

Sowunmi *et al.* 1992). Three were confirmed as cerebral malaria at post-mortem examination. The other two who survived had initial negative slides but further examination showed malaria pigment in white blood cells. One patient went on to have a positive smear for asexual forms of *P. falciparum* 12 hours later. A study of 55 adults with CM in Bangladesh found that on admission 24 (44%) had parasite counts $\leq 100/\ mm^3$ (i.e. 100/μL) although the multiplication factor they used was 75 (Waiz and Chakraborty 1990). They say in their article that cerebral malaria patients had on average lower parasite counts than patients with the other forms of severe malaria. For this reason, they suggest that the sequestration of malaria parasites in the brain may be reducing the parasitaemia detectable in the peripheral circulation.

To examine for these possibilities, a rapid malaria test (OptiMAL®) was used to assess patients who were slide negative and yet had features of altered mentation. One child admitted to Kabale hospital (December 2002) was assessed in this manner. Two thick smears were found to be negative for asexual forms of *P. falciparum* but the rapid test was positive for the same malaria species. By this time it was becoming evident that something was going on which we had not been prepared for. From then onwards cases with a presumptive diagnosis of cerebral malaria underwent microscopy and a rapid test. Despite this remedial action, it was not possible to find other cases of cerebral malaria maybe because it was too late into the study to do so.

During the pre-recruitment phase of the study health centres in the four study districts were sensitized about the project and on the need to refer suspected cases of cerebral malaria to the study hospitals if they were not able to manage them appropriately. District health teams were also alerted of the need to inform people during health education sessions of the importance of taking confused or unconscious patients to the nearest health centre or hospital as quickly as possible. In the course of the recruitment phase, leaflets were sent out to private clinics because it was thought that a small number of cases were going there for treatment. One of the popular private radio stations in Mbale town was used to make the residents aware that patients with cerebral malaria were being studied at the hospital and receiving optimal treatment that was given free-of charge. All these measures were employed to facilitate the referral of patients who were suspected of having

CM to the study hospitals and to reduce the proportion of sick people who are not captured by the formal heath sector. On the other hand, because its clinical features are frightening, it may be that sufferers are more likely to be taken to hospital than those with the other manifestations of severe malaria. How these factors affected the numbers of patients with cerebral malaria seen at the study hospitals is not clear and whether they affected children and adults equally or not cannot be elucidated. In discussing and interpreting the findings, the biases due to the small sample size are taken into cognisance.

6.2 Cerebral malaria in children and adults

In the following subsections, the results related to cerebral malaria in children and adults are discussed. I will address the frequency of cerebral malaria and age-of-disease onset, giving reasons for relevant findings or their absence. A detailed discussion of the commonest presenting features namely, fever, seizures and altered mentation, follows in order to corroborate the findings with those of other studies. In this way, an idea of the limitations of the study can be appreciated before more specific aspects of the findings are interpreted. Where possible, the differences in the clinical features of CM between children and adults will be elaborated since they have a bearing on the risk factors for neurological sequelae.

6.2.1 Frequency of cerebral malaria during the study period

The proportion of cerebral malaria among falciparum malaria admissions aged 1 to 70 years, and admitted during the 19 month period was 1.9% (100/5381). The proportion was higher at Kapchorwa hospital than at Mbale hospital. Likewise the incidence rate of 14 cases per 1000 falciparum admissions per year at Kapchorwa was higher than at Mbale hospital where it was 11 cases per 1000 falciparum admissions per year. These values are fairly similar to those observed at a) Mnero Hospital in Tanzania, in which the proportion of childhood cerebral malaria during the three year study period 1979-1981, was 0.8% i.e. 66 cerebral malaria cases from 7915 falciparum malaria admissions (Schmutzhard and Gerstenbrand 1984); b) University of Calabar Teaching Hospital in Calabar, Nigeria, where the proportion was 0.9% i.e. 75 children (15 years and below) with cerebral malaria from 8341 paediatric admissions with fever during the 30 month study period from January 1986 to June 1988 (Ikpatt, Asindi *et al.* 1990); c) Mangochi District Hospital and

Kamuzu Central Hospital in Malawi, where 199 children aged under five had CM (from 8600 children under five years of age admitted to both hospitals between 1 January 1994 and 31 December 1994), giving a proportion of 2.3% (Nkhoma, Nwanyanwu *et al.* 1999). The occurrence of cerebral malaria in these studies is similar even though the age groups and case definitions of cerebral malaria differ. Their values though are much smaller than the other studies that have been summarised in Chapter 2. The large variation in the frequencies of CM even between studies done in the same country illustrates the limitations of hospital-based studies in estimating the true occurrence of the disease in communities even if its occurrence is not equal. However, there have been no estimates of the incidence of cerebral malaria which would be the more ideal and comparable measure.

During the study period, the proportion of malaria admissions that were cerebral malaria was relatively higher in Kapchorwa hospital than Mbale hospital even though more numbers of CM cases were admitted to the latter. Malaria transmission is less stable in Kapchorwa than Mbale. A hospital-based study that used two hospitals in areas at different altitudes and different malaria endemicities (Kamuzu Central Hospital at 1,200m above sea level and Mangochi District hospital at 500m) found no difference in the proportion of CM among hospitalised children under five years of age between the two hospitals (Nkhoma, Nwanyanwu *et al.* 1999). The authors restricted their investigation to young children whereas if they had not, the proportion in the older age groups may have been different as the current study suggests. Snow *et al.* (1997) corroborate the findings here in a study at five sites in Kenya with different levels of malaria transmission. They noted that the period proportion of cerebral malaria declined significantly with increasing malaria transmission intensity.

Cerebral malaria frequency fluctuated during the study period from 1st January 2002 to 31st July 2003. The first rainy season in Uganda which is usually March to May had a greater number of cases compared to the later rainy season of September to November. The weather data from Mbale and Kapchorwa show that the rainfall in the earlier season is higher than that in the later season and the maximum and minimum temperatures are higher by a degree or two from March to May compared to September to November. This can explain much of the monthly variation in the

frequency of cerebral malaria. It is known that the occurrence of malaria in a population continues for one or two months after the end of the rains. Unfortunately, for this thesis, it was not possible to get the monthly frequencies of malaria admissions at the study sites and their weather indices for the study period to better explain the time variation in cerebral malaria admissions. The relationship between cerebral malaria occurrence and climate has been documented before in Tanzania where the seasons are similar to Uganda (Schmutzhard and Gerstenbrand 1984). Over the study period, the authors got the largest number of cerebral malaria cases in June (i.e. 15 cases) whereas in this study the largest number of CM admissions was in July 2002. Therefore it is very likely that most of the variation in frequency is explained by climate.

This study was hospital-based and the four sites are subject to different selective processes that affect the proportion of children with cerebral malaria who reach hospital. Factors such as distance to hospital, mode and cost of transportation to hospital, existence of user-charges at hospital, awareness of the need to take the patient to hospital, acceptance of conventional or tradition methods of treatment and the image of the hospitals, affect health-seeking behaviour. Three of the hospitals except Mutolere hospital, are government hospitals and were not charging user-fees at the time. St. Francis Hospital, Mutolere, is a missionary hospital and charges for its services, but it was the only hospital in the district that was known by the local population to be able to handle people who are very ill. Additionally, more than 95% of the population of Kisoro is Christian and would not have any religious reasons for not using the hospital. Despite making arrangements for cerebral malaria cases to be treated at no cost, the fact that it was known to be a charging facility will have made it less accessible than would have otherwise been the case. Kisoro hospital which is government-funded is about 15 km away from Mutolere hospital. It, at the time, did not have a functional laboratory and patients were managed according to presumptive diagnoses. The clinical staff there had agreed to refer patients to the study hospital and they were contacted often to find out if they were getting any suspected cases. Apart from a handful of suspicious cases who were not referred, cerebral malaria did not seem to occur in the numbers expected. Kabale hospital, which is situated in an area of similar malaria endemicity as Kisoro and Mutolere hospitals, was not getting cases of cerebral malaria either. Kabale hospital is the

referral hospital for that region and was not charging user-fees. In fact, there were indications that the residents of Kabale town where the hospital is based preferred to take very ill relatives to private clinics that had the drugs to manage them (which is why leaflets describing the study and encouraging referrals were also sent out to private clinics). The PI visited one of the private clinics with admission facilities in the town to determine if this was the case and was told by the doctor that they did see patients with 'cerebral malaria'. However, the diagnosis was made on the basis of altered mentation and a positive smear for *P. falciparum* and it was therefore not possible to confirm the claims. These observations suggested that in Kabale and Kisoro, outbreaks of severe malaria occur only during malaria epidemics.

The frequencies of cerebral malaria obtained here are probably underestimated. The denominators in most calculations of frequency are malaria admissions. If the diagnosis of severe malaria is presumptive (i.e. 'clinical malaria') and not microscopic then there is the issue of over-diagnosis of malaria. In addition, we know that a sizeable proportion of patients with severe malaria who require admission never get to hospital. This means that on the one hand there may be over-diagnosis and on the other, under representation. The significance of these inaccuracies will differ from population to population, however, it is likely that the denominator is also underestimated. Consequently, the estimation of the proportion of cerebral malaria based on the values used here even though not a valid representation of the true frequency in the population is a good estimate.

6.2.2 Age of cerebral malaria cases on admission

The age-specific frequency of cerebral malaria was 1.4% of malaria cases admitted (46/3364) in children aged 1-4 years, 1.9% (72/3789) in those aged 1-9 years and it was 1.8% (28/1592) in those 10 years and above (up to 70 years). This fairly even occurrence in the three age groups does not persist when one compares them by study hospital. The 5-9 year and 10-70 year age groups had the higher proportion of cerebral malaria cases in Kapchorwa. The incidence rates showed this same trend. The rate in the 5-9 year group admitted to Kapchorwa hospital was almost twice that at Mbale hospital. Interestingly, the incidence in the under fives admitted to Mbale hospital is greater than in Kapchorwa hospital. In the 10-70 year group, the incidence of CM was slightly greater in Kapchorwa than Mbale. The median age on

admission in Mbale was 48 months which was half the median age of 96 months found in Kapchorwa hospital. These differences were not unexpected. In fact, one reason for using hospitals situated in the highlands was to take advantage of this epidemiological observation in which the age distribution of cerebral malaria has been noted to be wider in areas with unstable malaria transmission (Newton, Hien *et al.* 2000). Examining studies that have looked at cerebral malaria in patients who are 10 years or below, those who found that CM was commoner in young children under five years of age (i.e. number of CM cases under five among total number of childhood CM cases) tend to be in areas with stable malaria transmission (Rothe 1956; Commey, Mills-Tetteh *et al.* 1980; Schmutzhard and Gerstenbrand 1984; Ikpatt, Asindi *et al.* 1990; Bondi 1992; Steele and Baffoe Bonnie 1995; van Hensbroek, Palmer *et al.* 1997; Idro, Karamagi *et al.* 2004). Those who have found CM commoner in children 5 years and over compared to those below have tended to be among indigenous people in areas of unstable malaria transmission (Ahmad, Moonis *et al.* 1986; Kamble, Raut *et al.* 2002). A study done at Eldoret, in the highlands of Kenya (altitude of over 2000m above sea level) on 23 consecutive CM cases aged 1 to 12 years found that the median age on admission was 9 years (range 2-11). The authors say that CM is one of the leading forms of severe malaria during epidemics of "highland malaria" in that region and affects older children rather than those under five (Esamai, Nabakwe *et al.* 1999).

The available studies on CM in adults have been conducted in areas with both high malaria transmission (Elamin 1981; Olweny, Chauhan *et al.* 1986; Sowunmi, Walker *et al.* 1993) and low transmission (Waiz and Chakraborty 1990; Niyongabo, Deloron *et al.* 1994; Kochar, Shubhakaran *et al.* 2002; Mohanty, Mishra *et al.* 2003). The authors who have been able to study adult cases in high malaria transmission areas have attempted to give reasons why CM occurred in that age group since it is not a disease that is often found in indigenous adults living in hyperendemic areas. These include yet unidentified genetic and environmental factors that affect the acquisition of clinical immunity; the effect of good mosquito control and chemoprophylaxis in the Copperbelt cities in Zambia in the 1960s that may have slowed the development of malaria immunity resulting in an adult population who are still susceptible to severe malaria; inadequate doses of chloroquine used to treat uncomplicated malaria which then progresses into severe

malaria; increasing virulence of *P. falciparum* strains; and decreasing susceptibility of *P. falciparum* to chloroquine.

The basis for the relationship between age of disease and malaria transmission is an immunological one. It is thought that clinical immunity to severe forms of malaria develops rapidly in children resident in high transmission areas. Consequently by the age of ten, a child should have developed sufficient immunity to protect him or her from cerebral malaria and the other forms of severe malaria (Marsh, English *et al.* 1996; Cegielski and Warrell 1997a; WHO 2000; Murphy and Breman 2001; Snow and Marsh 2002). Children resident in low transmission areas would take longer to develop the same repertoire of immune responses to offer similar protection. As a result, severe malaria occurs both in children and adults in malaria-epidemic prone regions (Kiszewski and Teklehaimanot 2004) and in adults whose previously competent immunity is diminished for one reason or the other as is the case in pregnant women (Foster 1996). This best explains why the CM cases admitted to Kapchorwa hospital, which serves a population living an area of unstable malaria transmission are older than those admitted to Mbale hospital. By design therefore, the multi-centre nature of this study has allowed both children (defined here as those under ten years of age) and adults (defined here as those aged ten years and above) with CM to be enrolled.

6.2.3 Presenting clinical features of cerebral malaria in children and adults

To ensure consistency and reduce interviewer bias, the ten common symptoms of severe malaria were listed and asked for using close-ended questions at Level 1. From these inquiries, fever (87 cases) was the commonest symptom reported followed by convulsions (75 cases). This is expected because one of the eligibility criteria was a history of fever or convulsions as they are the commonest symptoms that patients with cerebral malaria are likely to present with. Loss of consciousness (66 occasions) and confusion (56 occasions) were the next frequent, in some cases the latter described as preceding the former in a continuum of altered mentation. Loss of appetite and headache were mentioned in just over half of the cases and were more likely to be noted in adult cases than children ($p<0.05$). Adults are able to express their *'dis-ease'* more capably than children and consequently those symptoms that require one to complain or express, such as headache, are more likely

to be mentioned by the adult cases than children. Other symptoms, cough, rigors/chills also differed significantly between children and adults ($p<0.05$).

Differences in the symptoms of cases seen at the two study hospitals are probably related to age because they also differed in a similar manner between children and adults (Kapchorwa cases on average being older than Mbale cases). A few additional symptoms were noted at Level 2 because at that level, doctors asked relatives for the main complaints their patients had before coming to hospital. These were general body weakness, loss of speech (aphasia), and pain in the neck, chest and abdomen. The loss of speech is a more specific indication of cerebral dysfunction but is a rare complaint. A detailed discussion of the three commonest symptoms, fever, altered mentation and convulsions follows because they are directly or indirectly on the postulated causal pathways for neurological sequelae.

6.2.4 Fever

Axillary temperature was used to estimate the core body temperature as described in the methods section. Although this is not the best way of doing so, it was used because it was the safest and most convenient method in that setting. To improve the accuracy of measurements, digital thermometers were used instead of the mercury ones that are routinely used in Ugandan government hospitals. In addition, digital thermometers have built in timers enabling the nurse or doctor to consistently take the measurement for a uniform period of time in all cases. On the first measurement of body temperature, 63 cases had a normal body temperature and 37 had above normal temperatures. This contrasts with the proportion who gave a history of fever. It is well known that the body temperature has diurnal variation and in malaria can fluctuate in a short span of time (Rooth and Bjorkman 1992). One accurate measurement is not a precise reflection of the true magnitude and impact of fever on the body. An average of several measurements would give a better representation of the true value. However, all study patients received the antipyretic paracetamol as part of their treatment. Other measures such as tepid sponging were also done. These interventions alter the degree of fever in patients at different rates. For these analyses it was decided to use the first measurements of temperature taken before antipyretics were given. In conjunction, the fever clearance time, which is the period from the onset of treatment to the time when the body temperature returns to normal

levels (in this case 37°C) for 48 hours, was measured. This provides an estimate of the rate at which patients were able to get rid of their fevers having received appropriate doses of paracetamol. One advantage of using fever clearance times is that it does not depend on the precise temperature measurements but rather on a series of above normal values over time. A disadvantage of the fever clearance time is that it can only be calculated in patients that survive long enough to clear their fever for the specified duration. Axillary temperatures were measured six-hourly, although this was not always the case, and recorded in the CRFs to one decimal place as given by the digital thermometer.

The mean body temperature on admission for all cases (n=100) was 38.1 °C. The mean fever clearance time was 2.8 days (95% CI 2.4-3.2) and the mean total fever clearance time was 5.5 days (95% CI 4-6.1). Fifty percent of cases with fevers were able to clear their fevers within 2 days. There was no association between body temperature and the fever clearance time either as continuous variables (assessed by correlation and regression) or categorical ones (assessed by Fischer's exact test). Walker *et al.* (1992) who studied 61 patients with cerebral malaria and a mean age of 5.7 years (±3.2), obtained a mean fever clearance time of 59.8 hours (±33.6) in fifty survivors which is similar to the value in this study. They do not mention the average core or body temperature of their patients neither do they state if an antipyretic was given to children with fevers[†].

Definite cases had a mean body temperature of 38.4°C (95% CI 38.1-38.7) which was higher than the value for *probable* cases, 37.7 (95% CI 37.4-38.1). The difference was statistically significant and may illustrate the severity of disease in the two groups. Patients with DCM had an average fever clearance time that was one day longer than patients with PCM, although the study was not able to detect it as significant at the alpha level. Unfortunately, Kamble *et al.* who also divided patients with CM in to *definites* and *probables* did not give the average body temperatures of patients to see how this compared (Kamble, Raut *et al.* 2002).

[†] Tepid sponging and fanning were employed to cool patients with hyperpyrexia (>39°C) although the effectiveness of these methods is questionable.

The mean body temperature was similar in cases seen at each study hospital as well as between children and adults. However the fever clearance time was different between children and adults and between study hospitals. Children took on average 3 days to clear their fevers compared to adults who took 1½ days (P = 0.02). The cases admitted to Mbale hospital were younger than those at Kapchorwa, which influenced the fever clearance times of cases at both sites. The children examined at Ibadan by Walker's group, had an average fever clearance time that was closer to that of the children in this study than adults. The difference noted here therefore may be a real one.

6.2.5 Seizure activity

Convulsions were more frequently reported among *definite* cases than *probable* ones (P = 0.06). There was no such difference between children and adults or between study hospitals. Of those with a history of seizures, referred to as reported seizures, 41 cases (55%) also had seizures while in hospital that were seen by medical staff, referred to as witnessed seizures, and of those who did not have reported seizures, 20 cases (80%) did not have witnessed seizures. These proportions are similar if one looks at children and adults separately and does not suggest that mothers may be over-reporting seizures in order to get more urgent treatment for their ill children. The proportion of children and adults who had witnessed convulsions was not significantly different (47 and 43% respectively). Febrile seizures are the commonest kinds of seizures in children aged less than five years but do not appear to have been responsible for seizure activity in this population. The only three children in this age group with hyperthermia had witnessed seizures. All three cases were *definite* cases. There was no association between age (as three categories) and temperature amongst cases who had seizures.

It is noteworthy that the clinical seizures described in this study are of the tonic-clonic type which are visible and easy to detect. The atonic or subtle kind in which there are underlying epileptiform brain discharges but no visible jerks are difficult to detect unless one has a high index of suspicion and EEG facilities. Worse still is the condition referred to be Crawley *et al.* as "electrographic status epilepticus" in which there are continuous electrical discharges lasting for 30 minutes or more on EEG with no apparent clinical manifestations (Crawley, Smith *et al.* 1996; Crawley,

Smith *et al.* 2001). They go on to warn that subtle seizures may go undetected the more so in busy and understaffed health units where most children with CM are admitted. None of the study hospitals had access to EEG facilities and were all busy units; this may have resulted in an underestimation of the proportion of seizures in this case series and misclassification of some cases. The indications from the studies are that patients with "electrographic status epilepticus" or subtle fits have a poor prognosis if their situation is not managed with appropriate anticonvulsants. Ten study patients did not recover, of whom three had reported convulsions and one had both reported and witnessed convulsions. It is possible that seizures would have been recorded more frequently if there had been EEG facilities.

In the analyses the number of witnessed fits during the first episode of seizures was considered (one episode being any number of seizure events followed by a post-ictal phase). Among those who had witnessed fits there was no difference in the median number of fits in *definite* and *probable* cases. Nor was there a difference in the number between Mbale or Kapchorwa hospitals. The significant variation was between children and adults (P = 0.01). Children (n=34) had on average 3 (95% CI 2-4) witnessed seizures compared to 1 in adults (n=12). These findings were based on the number of fits in the first episode of seizures determined by a variety of clinical staff and are therefore subject to measurement errors that could have affected the accuracy of the numbers recorded. If seizures are an important risk factor in this population as has been shown in others then their greater occurrence in children will predispose them to the outcomes.

The proportion of children (age range 9 months to 11 years) with fits in a study done at Kilifi, in Kenya was 62% (40/65). The median number of seizures was 5 (range 1 and over 20) during the entire clinical course of their illness. Eighteen children (28%) had one or more episodes of status epilepticus (Crawley, Smith *et al.* 1996). The limitation in making comparisons between other studies is the manner in which seizures are counted and over what period. Most studies simply note whether a patient has a seizure or not and only a few count the number of seizures (Ahmad, Moonis *et al.* 1986; Olweny, Chauhan *et al.* 1986; Molyneux, Taylor *et al.* 1989; Ikpatt, Asindi *et al.* 1990; Steele and Baffoe Bonnie 1995; Olumese, Gbadegesin *et al.* 1999; Kochar, Shubhakaran *et al.* 2002).

The median of the duration taken to control seizure activity in hospital, which I have called the seizure stoppage time, was 2 days for children and 1 day in adults (n=44). Although this difference was not statistically significant, it is further indication of the greater occurrence of seizure activity (either as number of fits or number of days with fits) in children. The median total seizure stoppage time (n=81) which is a summation of the number of days with reported seizures and witnessed seizures was 2 days for both children and adults. Adults were less likely to report seizures than children, 71%, (20/28) compared to 78% (56/72) respectively although on average they both had symptoms of seizures for a similar duration (median of 1 day and range of 1-5 days).

6.2.6 Altered mentation

All cases had some degree of altered mentation because this was one of the requirements for inclusion. Its depth ranged from confusion to unrousable coma. Patients who had unrousable coma were classified as DCM if they also met the other requirements. Two methods were used to determine coma depth on admission and to monitor progress. A simple tool that focussed on motor function by determining if a patient was able to localise a noxious stimulus or one of the coma scales, BCS or GCS, that assessed visual and verbal function in addition to motor function. The simple tool was employed because it could be used by both nurses and doctors, it was easy to teach, easy to learn and was sufficiently reliable and accurate for purposes of monitoring the progress of an unconscious person (Sternbach 2000).

Fifty-two cases were not able to localise pain at Level 1 (by a nurse) and seventy-five cases at Level 2 (by a doctor). The assessments by the nurses were usually done as soon as the patient was admitted (the target was to do so within 2 hours of admission) before the doctor's assessment (the target was within 6 hours of admission). It is difficult to say whether the change in proportions was due to the experience of the assessors or due to disease progression between one assessment and the next. To improve the reliability of assessments and reduce interobserver disagreement, there were training sessions for both nurses and doctors on how to use the simple tool and the two coma scoring methods (Rowley and Fielding 1991). The sessions were conducted by very experienced neurologists and repeatedly during the

course of the study, the senior consultant paediatrician in Mbale and the PI while at any one of the study hospitals, observed how the clinical teams measured coma depth. New team members were trained on neurological assessments by either the PI or one of the senior clinicians.

At Level 1, the proportion of children that were not able to localise pain on the simple tool was 53% (38/72) which was slightly greater than the proportion of adults, 50% (14/28). At Level 2, the respective proportions were 81% (58/72) and 61% (17/28) which was quite a large difference between both groups (P = 0.07). The BCS was used to assess children aged five years or below and the GCS was used for the older patients. On the BCS a score of 2 or less corresponds with unrousable coma, the depth required for DCM. On the GCS, the corresponding cut-off is not very clear. It appears to lie between 8 and 10. Using the lower value as the cut-off then a total of 50 cases were in unrousable coma on Day 0, their first measurement with either scale. This is lower than the number detected with the simple tool. Combining the scores from both scales, 67% of child cases (40/60) had scores corresponding to unrousable coma compared to 30% of adult cases (8/27). The findings are that more adults were admitted in less severe coma than children. One reason for this is that adults with a history of convulsions even without the appropriate depth of coma are considered to have cerebral involvement (PCM) because of the relative rarity of other conditions that cause sudden convulsions in a non-epileptic adult. Checking for this among the adult cases who scored over 8 on the GCS, it was observed that of the five adult cases who scored 14 the highest score observed on first measurements, three had a history of seizures and another had both a history and one witnessed seizure (there was no score of 13 on first measurement). Fourteen adults scored between 9 and 12 and of these nine had a history of convulsions and twelve had witnessed seizures. Therefore, adults with altered mentation but could localise pain (a depth not associated with mortality or neurological sequelae) were likely to have seizure activity (a factor known to be associated with mortality and neurological sequelae) which made them fit the PCM case definition.

The duration taken to regain consciousness, the coma recovery time varied from a minimum of 1 day (cases that took less than 24 hours were categorised as one day)

to a maximum of 12 days (n=67 survivors with complete information on coma duration). 22 cases (33% of 67 survivors) were conscious within two days. In two other studies, the corresponding figures were 74%, 22 patients out of 43 children (Commey, Mills-Tetteh *et al.* 1980) and 61%, 14 patients out of 23 children (Esamai, Nabakwe *et al.* 1999). The total coma recovery time which refers to the number of days before admission for which a person was not conscious plus those spent in hospital before regaining consciousness varied from 1 day to 15 days. Cases seen at Mbale hospital on average had a longer duration for both the coma recovery time and the total coma recovery time. *Definite* cases as would be expected, took longer to regain consciousness than *probable* cases but these differences were not large enough to be statistically significant. Children, like adults, took on average 3 days to recover from coma. Quinine given at the referring health centre prior to admission could have improved the speed of recovery but the distribution of quinine use before admission was similar between children and adults, study hospitals, *definite* and *probable* cases. Therefore the differences in coma duration even though not large enough to be statistically significant in this study appear to be associated with some factors that are not related to quinine use.

6.2.7 Mortality and Prognostic factors

Ten cases died while in hospital and eight cases had their hospital stay terminated by a relative or attendant. As described in the results, it is more likely that those who were prematurely taken away survived meaning that the case fatality in this case series was 10%. This estimate is lower than most of those given in the background section of this thesis. Herein lies another limitation of hospital-based studies which are more likely to receive patients that are at the upper extreme of disease severity. Some of the studies on this disease have been done in research-oriented health units or large tertiary hospitals which could have been even less accessible to the catchment communities. In this study, much effort was put in encouraging relatives to take their unconscious patients to the study hospitals which invariably were the only health units with the facilities to handle their treatment adequately. This may have resulted in the enrolment of a more heterogeneous population of CM patients with respect to risk factors and severity. If the sensitization of the health practitioners at the lower level health units influenced improved their speed of

referral, then more cases may have gotten to hospital in time for medical intervention to achieve the desirable goal of a cure.

Anecdotal evidence from the hospital staff suggests that the interventions that had been put in place during site preparation caused a decrease in mortality attributable to clinical cerebral malaria. These interventions were; training of the staff for the project, better patient triage, increasing the availability of drugs and associated items such as intravenous giving sets, allowing study nurses to initiate treatment, and improving the speed of laboratory evaluations on a 24-hour basis. It cannot be ignored that the staff were more motivated because they were participating in an activity which they saw having beneficial results on their output. A study of this nature had not been carried out before at any of the study hospitals and additionally, most of the nursing and laboratory staff had not been on refresher training courses since their graduation. The combination of these had a positive impact on mortality due to cerebral malaria, and possibly severe malaria in general. It was because of the possibility of this kind of impact that district hospitals were chosen in preference to New Mulago hospital the only national referral unit.

Thirty-eight cases had received quinine at another health facility within 48 hours before admission, which is a useful intervention in reducing mortality. One case who died had been given quinine before admission whereas the others had not. The association between quinine use and mortality was demonstrated in both univariate and multivariate analyses. A positive history of quinine use within 48 hours before admission was a good prognostic factor. Although this association was based on very small numbers and was not significant at the 0.05 alpha level it is of clinical relevance. If it is beneficial for referring health units to give a dose of quinine (intramuscularly since the facilities for intravenous administration would not usually be available at lower levels) before sending the patient off to a higher level unit, then the pros and cons need to be evaluated. During my review of the literature on cerebral malaria I did not come across a study that has examined this link.

A greater proportion of deaths were children under five years (6 children / 10 deaths). This is not a new finding and has been elaborated upon in Chapter 2 and can affect the rate of neurological deficits in children by decreasing the numbers at risk.

Children aged under 3 years have been found to be at greater risk of mortality compared to those over that age (Walker, Salako *et al.* 1992; Jaffar, Van Hensbroek *et al.* 1997). The same trend was found in this study although the association was not an independent one in univariate analysis. Adjusting the crude OR association by case definition or centre, did not have any effect. The multivariate logistic models, Models 1, 2 and 3, showed a smaller OR in adults compared to children. In Model 3, which was restricted to *definite* cases, the association between age and mortality produced a P value that was almost significant at the 5% alpha level. The current study would only be able to detect as statistically significant a large difference between the two age groups which it almost did. A larger sample size would have elucidated this association.

Mortality was higher in Kapchorwa than in Mbale hospital. Mbale hospital is better equipped and better staffed than Kapchorwa but because it is a referral hospital it is very busy. It was not possible to confirm the diagnoses of all the deaths that occurred among patients admitted with non-traumatic coma during the study period. It is possible that a proportion of deaths were not captured by the study systems in place and if there was a non-random difference in the numbers between hospitals then the findings may not reflect the true values for hospital-specific mortality. In the multivariate model, Model 1, the OR was 1.63 (95% CI 0.38-7.10) but this became larger, though even less precise, once the model was restricted to *definite* cases amongst whom the deaths occurred.

Cases that did not survive formed a special group in another way. As described in the methods section, a category that consisted of observations without values was created to enable consistent numbers of cases during the various kinds of analyses. Missing data at Levels 1 and 2 containing this category often were because of failure to obtain and/or record information in cases that died. This was not expected but makes sense because one of the issues that was stressed during the training sessions was that prompt and appropriate case management was of greater priority than collecting data. Team members were expected to diagnose (take relevant routine laboratory specimens to confirm presumptive diagnoses), and start treatment (definitive and supportive) after which they could collect any additional information that was for research purposes. This was stressed repeatedly and much time was

spent on improving patient triage within the hospital as well as improving the movement of specimens to and results from the laboratories. If the cases that died presented in fulminating disease then the staff would not have had the opportunity to fill in their CRFs before their demise. This seems to have been the scenario.

Contrary to the literature, a history of any number of seizures was associated with a smaller OR for mortality than no such history. The same trend was found for witnessed seizures. These associations are based on small numbers and as explained earlier were not expected. Other studies have shown a greater frequency of convulsions (either witnessed or reported) in patients who did not recover from CM, which contradicts the results here (Endeshaw and Assefa 1990; Walker, Salako *et al.* 1992; Jaffar, Van Hensbroek *et al.* 1997). If this is an error then it is due to failure to detect or record subtle seizures or 'electrographic status epilepticus'. If on the other hand this is a reflection of the association between convulsions and mortality in this population then it could be because the patients who died did so before they were able to have fits. In other words, to have seizures they needed to survive for long enough for them to manifest. Though the numbers are small, the trend for both reported and witnessed seizures are in the same direction suggesting that some other factors may be at play that were not measured in the study. The manifestation of clinical seizures in hospital remained independently associated with the outcome in multivariable analyses, Models 1, 2 and 3.

The doctors usually examined the cardiovascular system in all study cases. For this purpose Littman® stethoscopes (paediatric and adult versions) which are renowned for their sensitivity were provided for this purpose. The detection of extra heart sounds such as, murmurs, thrills, bruit, third and fourth heart sounds were noted and their presence was associated with a greater risk of mortality compared to their absence. More deaths were noted in the category which had missing information on this variable. As explained previously, this is because of the practical reality of managing very sick children in a very busy setting. The patient may either have died before the doctor was able to carry out a complete examination of the body systems or the doctor may have carried out the examination but because of the seriousness of the patient's condition had to proceed with other aspects of case management and not had the opportunity to record his or her findings in the CRFs. Lacking

information on the presence of heart sounds was associated with death by an OR of 8.50 (95% CI 8.50-1.75). The clinical value of this finding is limited, however in epidemiological terms it is relevant. If all the cases with missing data on this variable had extra heart sounds then the OR would be modified away from the null; conversely, if they did not have extra heart sounds then the OR would be modified towards the null. The common conditions that produce extra heart sounds when associated with cerebral malaria increase the likelihood of death. Thus, a clinical sign in the heart that is associated with increased mortality may have been missed in non-survivors[‡].

The association between random blood glucose on admission and mortality was one that had been anticipated because it had been documented previously in other studies (Brewster, Kwiatkowski *et al.* 1990; Endeshaw and Assefa 1990; Walker, Salako *et al.* 1992; Jaffar, Van Hensbroek *et al.* 1997) except one (Niyongabo, Deloron *et al.* 1994). The largest study to-date on childhood cerebral malaria which examined the predictors of fatal outcome in 624 children found an OR of 5.8 (95% CI 3.0-11.2) in children that had multiple episodes of hypoglycaemia i.e. blood glucose level < 2.2 mmol/L (Jaffar, Van Hensbroek *et al.* 1997). The cut-off they used is the same used in this study. However, the results here are based on one random blood glucose measurement. Those without glucose measurements had the higher OR of 6.25 (95% CI 0.64-61.00). Incidentally, the only study on adult CM found similar mean plasma glucose levels in fatal and non-fatal cases, and no case had hypoglycaemia i.e. < 2.2mmol/l (Niyongabo, Deloron *et al.* 1994). When the crude OR was adjusted for age (as two categories) it did not affect the estimates.

Another factor that was associated with mortality was the parasite count on Day 0. Compared with those having counts in the lower category of 50,000 parasites/μL or less, the OR was 4.46 (95% CI 0.78-25.67) for counts over the cut-off and 6.25 (95% CI 0.87-45.14) for those who did not have a count done. Again these values are based on small numbers making the estimates imprecise. However the trend of an increased risk with an increased degree of parasitaemia is one which is already documented although in studies that have been situated in areas of more stable

[‡] One child with CM (ID 2040) who had a murmur due to a cardiac lesion developed severe neurological sequelae

malaria transmission where on average the patients have had higher parasite densities. Jaffar *et al.* (1997) obtained a smaller and more precise OR of 2.2 (95% CI 1.2-3.8) using a cut-off of ≥ 500,000/μL. It would not have been possible to use a similar one because only one case had a parasite count ≥ 500,000/μL. The mean (geometric) parasite count in 85 cases evaluated for parasitaemia was 15,973/μL (range 131-590,400). Although the mean parasite count in Kapchorwa was higher than in Mbale, 26,215/μL (95% CI 10,581-64,956) compared with 12,683/μL (95% CI 6,836-23,531), much higher parasite densities were expected. If all fatal cases had been evaluated it is possible that this would raised the mean count because of the positive association between parasite density and mortality. *Probable* cases had a higher parasite count than *definites* although the difference was not statistically significant. Adjusting for centre and age separately did not have any significant effect on the crude ORs. Adjusting for them simultaneously (and quinine use before admission) in the logistic model and using only *definite* cases, the OR for both comparison levels increased substantially.

Unlike the findings by other investigators already referred to in this section, this study was not able to find significant associations between mortality and a number of factors in univariate analysis. These are abnormal respiratory pattern, rapid pulse rate (≥ 160 beats/min), features of shock (cold peripheries), coma score of 0 or 1 on the BCS, white blood cell count ≥ 15,000/μL, severe anaemia (Hb < 5 g/dL), signs of decerebration or opisthotonus, creatininemia (> 265 μmol/l), bilirubinemia (> 50 μmol/l), and blood lactates > 5mmol/l. The main reason for this is that the power of this study was very small and some of the effects which are not very large would not have been detected.

6.3 Neurological sequelae in children and adults

The following paragraphs will concentrate on the neurological sequelae of cerebral malaria. The findings will be interpreted within the limitations of the study. To obtain a bearing on the validity of the results, the findings will be elaborated within the context of other studies and where possible some of the underlying reasons for any differences in sequelae in children and adults will be mentioned. Errors and biases that may have had an influence on the results will be described or referred to if already mentioned elsewhere.

6.3.1 Frequency and types of neurological sequelae

Sequelae were detectable in 35 survivors at discharge or follow-up (range 1 week to 39 weeks) and were motor-sensory in 22 survivors, cognitive in 7 or a combination of both in 6 survivors. The frequency of sequelae here is higher than in other studies because of the lower mortality and the timing of neurological assessment. In this study the first check for deficits was carried out at discharge (median duration of hospital stay was 7 days for survivors, range 3-48) at which time 23 survivors had noticeable neurological abnormalities. Some of the abnormalities that were later on detected as sequelae, developed during disease. There is no standard definition for the neurological sequelae of CM and that is why it was very important to have one for this study that was able to give a point during recovery at which the presence of neurological dysfunction became a complication/s. That point was when consciousness was regained (BCS = 5/5 or GCS $\geq$ 14/15) because it is by this time that a survivor can be discharged home in which case any aspect of neurological function that is still impaired will become a deficiency to the individual and may even be incapacitating.

Twenty-two cases with sequelae (detected at discharge and follow-up) were treated at Mbale hospital (i.e. 31% of all Mbale cases) and thirteen cases at Kapchorwa hospital (i.e. 43% of all Kapchorwa cases). On the other hand, the proportion of survivors with sequelae at discharge who were treated at Mbale hospital was 27% (17/70) which was slightly higher than at Kapchorwa hospital, where the value was 23% (6/30). The proportion of cases that attended follow-up visits was significantly higher in Kapchorwa (92%, 24/26) than Mbale hospital (44%, 28/64) which will have resulted in an inaccurate estimate of the number of Mbale cases that developed deficits after discharge. The major reason for the higher follow-up rate in Kapchorwa is that it was possible to arrange for a nurses to visit the homes of children who failed to come for their scheduled visit. In Mbale it was not possible to do so. Instead, announcements were aired on one of the radio stations with wide coverage in the district reminding parents (without using personal identifiers) whose children had been enrolled into the study to bring them for follow-up. All survivors were included into the study after obtaining informed consent. During this process and at discharge, the need to attend follow-up was emphasised. It was also made

clear that a refund for transportation costs (to and fro) would be given at each visit. Mbale district has a better transportation network (roads and public transport) than Kapchorwa. The populations in both districts are fairly similar socio-economically and any constraints operating at this level would have been random. An idea of the factors that prevented parents from bringing their children for visits comes from the findings made by the nurse/s who made home visits. Some parents did not have any money to make the trip to hospital; some mothers were very busy and could not find the time to make the long journey to hospital; and some did not have any special reason. Fortunately, none of those who had not come for their scheduled visits at Kapchorwa and were later traced and assessed, had gross or worrying sequelae. It is clearly essential in studies of this sort to make provision for home visiting for follow-up.

Overall, the frequency of sequelae among survivors tended to be higher in the older ages, 28% (11/40) in 1-4 year group, 54% (13/24) in 5-9 year group and 42% (11/26) in $\geq$ 10 years (not statistically significant). At discharge the frequencies were 20% (8/40), 38% (9/24) and 23% (6/26) respectively (not statistically significant). If survivors that attended one or more follow-up visits were the denominator then the frequencies of deficits detected during follow-up in the three age groups were, 24% (5/21) in young children, 41% (7/17) in older children and 50% (7/14) adults (P value not significant). Nineteen survivors aged 1-4 years (48%, 19/40), 7 survivors aged 5-9 years (29%, 7/24) and 12 survivors aged $\geq$ 10 years (46%, 12/26) did not come back to hospital after discharge. Even with these losses to follow-up they did not substantially change the frequency of sequelae by age group from the frequency at discharge. If there had been fewer losses, and if the findings of the nurses during the tracing of subjects lost to follow-up in Kapchorwa can be extrapolated to Mbale, then there is little reason to expect the age trend in the occurrence to be very different from what was found. The data rather suggest that any change in the frequency or persistence of sequelae by age occurs between those above and below 5 years. This hypothesis could usefully be addressed in a larger study.

I think is important to consider age-group frequencies of sequelae in the context of age-group mortality. Young children had a lower frequency of deficits but a higher frequency of mortality. This may indicate that the age groups with lower mortality

have a greater number of survivors at risk for complications. Hospital-based studies are prone to selection bias and if cases with severe disease (such as very deep coma or have additional conditions) are selectively more likely to be brought (or referred) to hospital then a larger number of survivors who would have had less severe illness are being excluded and not studied. Unfortunately, my study did not have sufficient power to make comparisons between those with severe and less severe disease in order to examine this hypothesis. One objective of this study was to elucidate the frequency differences of the neurological sequelae of CM in Ugandan children and adults. This could not be achieved with the sample size.

The types of deficits seen in this group are similar to those that have been described in other study populations. They ranged from mild severity to incapacitating. The motor-sensory deficits, which were detected by clinical examination and a number of tests, affected muscle tone and power, tendon reflexes, cranial nerves, coordination, vision and speech. Cognitive deficits were more difficult to detect. Their examination focussed on language, verbal comprehension, attention and memory using a combination of a primitive tool with two versions, one each for children and adults, and clinical assessment. The detection methods were not very sensitive or specific but for practical purposes in the setting of the study, some means of screening and differentiating survivors who 'potentially' had complications from those were 'potentially' free from complications had to be devised. Much information was gathered by taking a detailed history of the condition of the subject while at home. Mothers were asked to compare the state of the child or in the case of an adult case, a close relative that usual lives with him or her, before and after the episode of cerebral malaria. A list of closed-ended questions was used for this purpose as well as open-ended ones. The role of recall bias is likely to be small because it was not likely that the changes in behaviour once noticed would be forgotten within the short span of time between discharge and follow-up.

Sequelae occurred in 19 *definite* cases and 16 *probable* cases and were of even frequency in the two groups. Twenty-five children (71%) and ten adults (29%) were detected to have deficits (amongst a total of 35 cases with sequelae). However, the proportion of children who were detected to have deficits, 37% (25 of 72 child

cases), was not much different from that of adults, 36% (10 of 28 adults cases). Most of the adult cases, 7 cases, were seen at Kapchorwa hospital. Examination of the types of deficits found in children and adults did not show any trend.

6.3.2 Natural history and timing

At the onset of the study, the terms 'early-onset' and 'late-onset' neurological sequelae were used to define the timing of the sequelae of CM. It is now apparent that the latter term is misleading because some of motor-sensory sequelae that were detected during the follow-up period had persisted right from the illness itself (5 cases of 23 with motor-sensory deficits at discharge). In some instances new deficits were detected on the visits (5 cases) i.e. truly 'late-onset'.

Eighteen survivors (78% of 23 cases with motor-sensory deficits at discharge) who had deficits at discharge did not have them at the first (median 5 weeks after discharge) or second (median 9 weeks after discharge) visit. The manner in which follow-up assessments were conducted did not allow the true timing of the onset of deficits to be determined. Instead, their 'onset' was determined by the timing of the detection procedure. At the beginning of the study, follow-up assessments of survivors were not regular because i) the PI was very busy shuttling between study hospitals to make sure that cases were being enrolled and managed in the right way and ii) the cognitive tools were not developed until later. It was during this period that some of the survivors were lost to follow-up. The majority of subjects with deficits improved during the follow-up period a finding that has been observed in other samples followed up over a similar time frame (Molyneux, Taylor *et al.* 1989; Brewster, Kwiatkowski *et al.* 1990; van Hensbroek, Palmer *et al.* 1997). There did not appear to be any difference in the natural history of sequelae in children and adults. It is not possible to say whether this null result is a real one or due to the small sample and large numbers of losses to follow-up.

6.3.3 Independent risk factors for early onset neurological sequelae in children and adults

Among ninety survivors of cerebral malaria who were admitted during the study period a number of factors were highly associated with early-onset neurological sequelae. Some of these factors were independently associated with the outcome in

univariate analysis and even in multivariable analysis. Before going into a discussion of these factors, I would like to say that splitting the outcome into early and 'late' onset was relevant for several reasons. Firstly, the underlying causal mechanisms for neurological dysfunction may be different or have different levels of importance. Secondly, the associations with the two kinds of outcome are subject to different biases such as losses to follow-up which affects 'late-onset' deficits mostly. Ascertainment of the outcomes, involved different procedures; at discharge, motor-sensory deficits were looked for whereas during follow-up, both motor-sensory and cognitive deficits were sought. Finally, it is of clinical value to have an idea of the predictors of the two outcomes separately in order to develop appropriate interventions.

Factors that were independently associated with early-onset sequelae in univariate analyses are quinine use within 48 hours before admission, enlarged spleen, duration of coma (coma recovery time), and white blood cell count on admission. A longer duration of coma is a known risk factor for neurological deficits and has been documented in studies on this topic (Bondi 1992; Carme, Bouquety *et al.* 1993; van Hensbroek, Palmer *et al.* 1997) except in one investigation (Idro, Karamagi *et al.* 2004). In my small study a coma duration of 5 days or more was associated with a 6-fold increase in risk compared to $\leq$ 2 days. The brain injury that manifests as neurological sequelae is said to occur during coma. Consequently, longer exposure to coma will predispose to neurological deficits, as this study shows. In the multivariate logistic models, the coma recovery time remained highly associated with the outcome with little change in the OR for the three comparison categories after adjusting for the other variables. The association with the white blood cell count is not clear though. The study in The Gambia found a significantly higher white blood cell count in survivors with sequelae and those without (van Hensbroek, Palmer *et al.* 1997).

Quinine use prior to admission and splenomegaly have not been identified by other researchers. Quinine in above normal doses is known to have side effects that affect neurological function *viz.* headache, dizziness, visual disturbances (optic atrophy in severe cases), convulsions, tinnitus and deafness. This is one of the reasons why a history of quinine use is a contraindication for giving a loading dose at the

commencement of intravenous therapy. Fourteen cases (median age 6 years, range 1-18 years) had a history of quinine use and early-onset sequelae. One of these cases received a loading dose of quinine on admission and had deficits in tone, tendon reflexes, and ataxia. Of the three cases with visual impairment at discharge, two of them had received quinine in the 48 hours prior to admission. These findings do suggest a role for quinine when given prior to admission. Apart from this, there was no association between quinine administered in hospital and early deficits.

The detection of a palpable spleen (> 1cm below the left costal margin, maximum was 5 cm), produced an OR of 3 (95% CI 1-9) in univariate analysis. This value increased significantly in the logistic models. Kamble *et al.* (2002) found enlarged spleens in 8 Indian children (53%) aged between 1 and 12 years whereas Waiz and Chakraborty (1990) found the same feature in only 7% of their sample of 55 older cases of CM. Olweny *et al.* (1986) found splenomegaly less common in Zambian adult patients with cerebral malaria than controls who had other forms of malaria suggesting a protective effect. Nacher *et al.* (2001) on the other hand did not find this effect in their case-control study and on the contrary found it significantly associated with cerebral malaria. These studies have been in different epidemiological settings and they indicate that the role of the spleen in cerebral malaria, either beneficial or deleterious, is still not clear. An animal model has suggested its involvement in cytoadherence (David, Hommel *et al.* 1983) which would support its role as a risk factor for early-onset deficits.

Seizures in this case series were not found to be significantly associated with neurological complications. This is in contrast to the study done in New Mulago hospital (Kampala, Uganda) which found multiple seizures to be independently associated with neurological deficits (Idro, Karamagi *et al.* 2004). The largest and most reliable study on CM neurological sequelae also found a relationship between multiple seizures and outcome (van Hensbroek, Palmer *et al.* 1997). This finding therefore needs to be evaluated in a larger study in the Ugandan population before a valid conclusion can be drawn. The effects of total fever clearance time and haemoglobin concentration in the model are difficult to interpret. The perception of fever as a symptom is subjective. The ORs for total fever clearance time imply lower relative risks with longer duration of fever (as symptom and sign). The small

number of survivors with the outcome did not allow confounding and interaction to be properly assessed which may responsible for these findings. The method used to estimate the haemoglobin concentration is not an accurate one but it was the only method routinely available in the hospitals. In retrospect, to rely on this was an oversight.

Age, categorised as two groups, was not associated with the outcome in univariate or multivariate analyses. However, using the three age groups, older children were more likely to be at risk than young children. The confidence intervals for the OR for adults was very wide and did not give an indication as to whether their risk was higher or lower. One of the study objectives was to determine if the risk factors for sequelae differed between children and adults. To do this, a model restricted to each group would have had to be developed. This was not possible because of the small numbers of children and adults with the outcome.

6.3.4 Independent risk factors for 'late-onset' neurological sequelae in children and adults

The reasons for using survival analysis have been highlighted elsewhere in this thesis. Taking 'time-to-event' in to account allowed better appreciation of the data and had not been tried before on this outcome. In conducting the analyses, the underlying parameter for the risk of the outcome, the hazard, was not constant over the period of follow-up. Contrary to what was initially thought as the reason for this, the declining likelihood of developing deficits over time having survived, the outcome ascertainment process introduced a different reason. Rather than 'time-to-event' the hazard represented 'time-to-detection'. This is why the baseline hazard function increased over the follow-up time especially when the majority of events 'occurred' i.e. the first ten weeks. Taking cognizance of this, the results need to be interpreted with caution.

In this sample, a seizure stoppage time of more than 2 days compared to the referent group, 1-2 days, produced a HR of 4.80 (95% CI 0.82-27.97) in the more robust model, Model 2, that did not include the clinically relevant variables. Survivors that did not have seizures had a HR of 4.95 (95% CI 1.13-21.78). This implies that detection and development of sequelae is more likely in these two groups than in the

referent group. The numbers of events in the two seizure groups are small and as a result the findings are questionable and difficult to interpret. Whereas fever was not a determinant for early-onset deficits, a fever clearance time of more than 3 days was a risk factor for this outcome. This was not unexpected since it has already been identified as a risk factor by other researchers.

Survivors that had deficits at discharge were 8 times more likely to have late-onset deficits. This finding follows on from the natural history of neurological sequelae. It is of clinical importance for two reasons. First and foremost it emphasises the need for all survivors of CM to be examined for neurological dysfunction before they are sent home. Secondly, survivors who have detectable deficits at the time of discharge require follow-up. Adults had a larger HR than children but this was not statistically significant. The differences in the determinants of late-onset sequelae between children and adults could not be examined because of the small sample size.

Two biases that affect the internal validity of the above results are the influence of losses to follow-up and the reliability of the methods used to determine the presence of the outcome (motor-sensory and cognitive deficits). As mentioned before, efforts were made to facilitate survivors to come for outpatient reviews. It is more likely that survivors that did not do so were free from overt neurological complications. If this was the case, their exclusion affected the precision of the risk estimates. The reliability of the cognitive tool is low. It was used as a screening tool and not as a confirmatory one. It may have been more prudent not to combine subjects that were identified by the cognitive tool with those that had clinically detectable deficits. However, the reason for doing so was that the *a priori* one of the study objectives was to elucidate the determinants of neurological sequelae, without separating them into their broad types.

6.4 Methodological issues and Study limitations

In the following paragraphs I will highlight some aspects of the study methodology that had an effect on the results and give some factors that influence the interpretation and validity of the findings.

6.4.1 Study design, sample size and power

The major reason for embarking on this study was to investigate if there were differences in the characteristics of the neurological sequelae of cerebral malaria in children and adults in Uganda. This meant that sufficient numbers of children and adults needed to be enrolled in the study and followed up. A multi-centre design was chosen based on information obtained from hospital records and discussions with medical practitioners at potential sites. Study hospitals were situated in areas of low malaria transmission intensity or close to such areas in order to capture adult cases of cerebral malaria. Even with all the measures put in place to facilitate patient enrolment, the numbers remained low, far less than the records had showed. The design had to evolve from four-sites into two-sites with a longer recruitment phase. The small sample that was eventually obtained could not power the study to detect some of the effects which were envisaged or sought. This constraint was not limited to this study alone, as has been described previously.

6.4.2 Measurement of exposure and detection of outcomes

Age-of-onset of disease was the exposure of interest. Its measurement was based on information provided by a relative, who was often the patient's mother, that brought the patient to hospital. Two sources of information were used; i) reported age and ii) date of birth. Often the sources corroborated, at times only one source was given and in a few instances they did not match to within 3 months. More reliance was placed on the date of birth when it did not match with the given age. It is unlikely that recall bias affected age measurements and if it was present, did not have much impact on the analyses because age was used as a categorical variable.

The outcomes of interest were the three main complications of cerebral malaria namely, mortality, early-onset and late-onset neurological sequelae. Mortality was ascertained in hospital. A few cases were taken away from hospital without being discharged and their outcome with regard to survival had to be inferred from the data. Early-onset deficits were detected by physical examination. Motor-sensory deficits were sought at this level using a structured data-extraction questionnaire which the study doctors had been trained to complete. This method had a high sensitivity for detecting overt deficits but a low sensitivity for subtle deficits which

mostly went undetected, but are probably less worrying. Late-onset deficits comprised motor-sensory and cognitive sequelae. The examining doctors were aware of the study hypothesis but the influence that this source of bias had was reduced by standardising the assessment process and using structured questionnaires. The cognitive tool though not an accurate and reliable instrument was the best-available objective method that could be used in the setting at that time.

6.4.3 Role of measurement error

This type of error will have affected the clinical and laboratory data that accrued during the study more so because it involved more than one study site. In anticipation of this, a number of measures were put in place to eliminate it or reduce its magnitude. These include, training of team members in data collection and measurement procedures, standardisation of clinical assessments and laboratory evaluations, implementing quality control in the laboratory, using accurate and reliable equipment where possible, using similar reagents at the study sites, and taking repeated measures. Despite these, some measurement error will still have remained but was minimal since a number of valid associations that have been identified elsewhere were seen.

6.4.4 Role of misclassification bias

This bias mostly affected information on the outcomes and some of the explanatory variables. The result was a type II error that made it more difficult to find effects unless they had a large magnitude.

6.4.5 Confounding and Interactions

The small sample size and low frequency of the outcomes limited the ability to control for confounders and test for interactions. For example, there was an interaction between centre and age which was not accounted for in the analyses. Nonetheless, identifying some of the determinants of neurological sequelae was one of the study goals and did not require having to control for all possible confounders or assess all the potential interactions.

6.4.6 Other causes of neurological dysfunction in the study population

There are other non-traumatic conditions that can lead to neurological deficits in the study population. These include sickle-cell anaemia, HIV infection and AIDS, cardiovascular accidents, and epilepsy. It was important to ensure that the sequelae identified were a consequence of cerebral malaria and not due to these other diseases. A history of any neurological dysfunction or epilepsy was a reason for exclusion in the selection criteria. HIV infection was checked in a subset of the cases and found to be present in a small number of subjects (5 cases were sero-positive 2 of whom had deficits). However, they were asymptomatic and unlikely to be manifesting the neurological complications of HIV which more commonly occur later in the natural history of the disease (Brew 1993b; a; Brew and Currie 1993) when other symptoms of HIV infection would be emerging. Anti-retroviral therapy can cause neurological complications as well but is not accessible to the majority of the community.

Tests for sickle cell disease (SCD) were not carried out because of the unavailability of the necessary reagents. The number of positive tests for homozygous Haemoglobin S (HbS) which is responsible for SCD at the laboratory in Mbale is on average one or two cases per week (personal communication from the Senior Laboratory Technologist). It is unlikely that any of the one hundred cases falls into this category because the abnormal red blood cells (sickle-shaped) would have been seen in the thin films that were examined to type malaria parasites. In addition, the doctors were aware of the need to exclude this diagnosis and would have identified subjects with features of SCD during the clinical assessments or follow-up.

6.4.7 Generalisability of the study results

The results documented here are a good representation of the features of CM and its neurological sequelae in children and adults in the population from which the sample was selected. I say this because even with the low enrolment rate, the magnitude of sampling error within the catchment area of the hospitals was probably small. The majority of patients that did not reach the government health sector are likely to have been those that were very ill and died. Those that did get to any of the lower health units within the catchment area of the study hospitals would have been

recorded or known to the medical staff at the unit. The surveillance system to track down 'clinical cerebral malaria' during the study involved visiting these units (and private-owned ones), communicating with their staff and liaising with the district public health teams who visit the health centres and communities regularly. This did not find that much 'clinical cerebral malaria' was ending up elsewhere even with the tendency towards overdiagnosis. Those patients who are taken to traditional healers or private health units (very few in Kapchorwa) limit the generalisability of the results to the population that is managed at government units. The proportion of losses to follow-up in Mbale also affects the generalisability of the results on 'late-onset' deficits in that area but not those of the other outcomes. The improved quality of care and diagnosis that were provided to the study cases means that the situation in which cases were managed is not what may be found in other hospitals in the country. This is another limitation to the generalisability of the results. However, if the picture seen here is better than what is found in other hospitals then it does mean that the complications of cerebral malaria i.e. death and sequelae, are higher in other hospitals, and the findings here are underestimates of the frequency of sequelae of cerebral malaria.

Chapter 7

7. CONCLUSIONS

This small-scale multi-centre study of one hundred patients was able to determine that the proportion of cerebral malaria among malaria admissions was 1.9% (72/3789) in children and 1.8% (28/1592) in adults admitted to the study hospitals. The case fatality ratio was low, 10%, and young children under five years of age at the time of admission had the higher mortality. Thirty-five survivors were detected to have neurological sequelae of either the motor-sensory (22 survivors) or cognitive (7 survivors) or both (6 survivors). The proportion of survivors with neurological sequelae was slightly higher in adults, 42% (11/26) than children, 38% (24/64). The more striking age difference was the frequency of sequelae among survivors aged under five, 28% (11/40), and those aged 5 to 9 years, 54% (13/24). The types of sequelae identified in survivors at discharge and during follow-up were described in detail and there was no difference between types in children and adults. Deficits were present in twenty-three survivors at discharge (motor-sensory sequelae only) and 19 survivors that attended review visits (motor-sensory and cognitive sequelae). Deficits involving muscle tone (detected in 18 survivors), tendon reflexes (14 survivors) and muscle power (12 survivors) were the commonest at discharge, occurring in combination. Cranial nerve deficits occurred in 4 survivors and impaired vision in 3 survivors. Many of the deficits improved within ten weeks post-discharge though a few survivors with severe impairment still had them at the follow-up visits and new ones were detected. Impaired muscle strength (5 cases) was the commonest motor-sensory sequelae detected during follow-up. The commonest cognitive deficit either reported by mothers of survivors or detected by the cognitive tool was memory impairment which was found in 10 survivors. Other deficits either occurring singly or in combination were post-cerebral malarial seizures (2 survivors who attended follow-up), impaired speech (2 survivors), attention deficit-disorder (2 survivors) and problems with language and verbal comprehension (2 survivors). The natural history of sequelae did not differ between children and adults.

Some important determinants of the three outcomes of interest namely, mortality, deficits at discharge (early-onset deficits) and deficits during follow-up ('late-onset'

deficits) were identified by multivariate analyses. Those independently associated with mortality were quinine use within 48 hours prior to admission, seizures while on the ward and parasite count on admission. Quinine use within 48 hours prior to admission, duration of coma, duration of fever (days with a history of fever plus days in hospital with a high temperature) and splenomegaly were independently associated with early-onset deficits. The detection and development of late-onset deficits was associated with duration with elevated body temperature, duration taken to cease having seizures and the presence of neurological deficits at discharge. It was not possible to examine the determinants for the outcomes in children and adults separately.

7.1 Practical study benefits

The scientific contribution that this study has made on the topic has been elaborated in the preceding chapters. There were some benefits of the study that require mentioning because they are of practical value. I list them below:

1. Mortality of cerebral malaria dropped during the study. This observation was based on anecdotal evidence from experienced clinical and nursing staff. The interventions that resulted in this beneficial effect have been mentioned.
2. The management of cerebral malaria at the study hospitals was standardised and adapted from International manuals to create guidelines suitable for the local setting. These adapted guidelines have been incorporated into the Ministry of Health (MOH) guidelines for the management of severe malaria in Uganda (a copy of poster is in Appendix VI).
3. The use of the parasite count as a diagnostic and monitoring laboratory test has become more popular at the study hospitals. The Standard Operating Procedures (SOP) for diagnosis of malaria developed by the MOH recommends the estimation of the parasite count but its use was not widespread. The experience of its benefits in this study are an example that is being used in seminars and conferences for Laboratory practitioners around the country.
4. There is now an increased awareness of the neurological sequelae of cerebral malaria amongst the study team members and the parents of survivors. As a result, survivors are now asked to return for review in the outpatient clinics which was not usually the practice.

5. Experienced nurses can now make a thick smear for diagnosis and initiate appropriate treatment for cerebral malaria at the units that participated in the study. Prior to this, they had to wait for a doctor to request a blood smear and prescribe quinine before commencing treatment. As a consequence, patients get adequate treatment faster, which is one of interventions recommended for malaria control, namely "Prompt diagnosis and treatment".
6. The staff at the participating hospitals have picked up an interest in malaria research. A study of this quality and nature had not been conducted at any of the sites before, and possibly none of the neighbouring district hospitals. Much of the medical research is carried out at the bigger teaching hospitals and yet the majority of the population visit their nearest district hospital. Having been through this project, seen that it is possible and gained some research skills, some staff are keen to develop, seek funding and conduct their own studies.
7. Diagnostic and laboratory equipment that were procured by the funds for the study have remained at the study hospitals. The hospital administrators have committed themselves for their usage in the units where they were placed during the study.

7.2 Areas for future research

In the course of this research project a number of areas for further study have been identified. These are listed below:

1. Contrary to the findings by other researchers, seizures were not associated with an increased risk of mortality or neurological sequelae. Subtle seizures may be occurring undetected and subsequently remaining untreated which can lead to poor prognosis if there is a link between seizure activity and death or complications.
2. There is need to elucidate the relationship between malaria parasite density and the manifestations of severe malaria in the south-western region of Uganda, specifically Kabale and Kisoro districts. These are areas that are prone to malaria epidemics with populations that are not immune to malaria. The expectation in such groups is high parasite counts because of their immunological naivety. This did not appear to be the case and there may be factors responsible for this. It is important to study this to improve the methods for diagnosis and determine if there are any implications for treatment.

3. The cognitive tool developed for detecting cognitive dysfunction requires more piloting to determine its usefulness in Uganda. At present, no tool exists for that purpose and yet as has been shown here, survivors of cerebral malaria do have cognitive sequelae that need to be managed. The tool is the foundation upon which more sensitive ones can be developed.
4. A number of patients that were tested for HIV-1 had discordant results on two ELISA tests. This has major implications for practical HIV control in Uganda because more often than not, one ELISA test is used at many of the district hospitals for screening for HIV. Why was this the case and does the combination of severe malaria (cerebral malaria in my study) and HIV have any impact on the diagnosis of the other, in the Uganda population.
5. The spatial risk factors for cerebral malaria require examination. Factors such as altitude, distance to health centre, and clustering of patients, to mention a few will help determine the populations are risk and very importantly the locations of patients that are not being captured by the health systems. In the course of my fieldwork, I collected dried blood spots from children along the slope of the Elgon ranges in Kapchorwa district. I intend to use these specimens to find out the altitudinal limits of malaria in the area at that time. I have also been able to obtain digital maps of Mbale and Kapchorwa districts and will use them to examine if the cases enrolled in this study had any obvious spatial characteristics.
6. There appears to be some important differences in the characteristics and complications of cerebral malaria in younger and older children, and adults in Uganda. A confirmatory study on this topic is needed and can help to shed more light on the pathogenesis of disease, brain injury and neurological sequelae with the objective of improving case management and prevention of complications. To do this, there is need to improve the sampling fraction and study a greater proportion of patients with cerebral malaria. A further study should not focus on cerebral malaria alone but should include the other central nervous system infections and compare the determinants of their early complications. This study has demonstrated that a major risk factor for the detection and development of deficits within ten weeks after discharge is the presence of neurological complications at discharge. The challenge therefore for the future, is to find interventions that reduce mortality and prevent the immediate complications.

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APPENDIX

Appendix I: Data collection tools, Information sheets, Consent forms

Copies of the following data collection tools are included here. They have been printed separately to maintain their layout and as a result the page numbers do not follow from the rest of this document. The following are contained herein.

- Checklist 1 and Form 1
- Checklist 2 and Forms 2, and 3
- Observation chart
- Forms 4, child and adult versions
- Forms 5, child and adult versions
- Information sheets (English and translated)
- Consent forms (English and translated)

Pages Missing not Available

260 – 334

Insert copies here without changing page numbers. Restart page numbers after

Appendix II: ***Aide memoirs***

Copies of *aide memoirs* used are provided here (except the guidelines for the management of cerebral malaria which are listed in the methodology). They have been printed separately to maintain their layout and as a result the page numbers do not follow the rest of the document.

- How to measure blood pressure using an automatic sphygmomanometer
- How to measure blood glucose using a glucometer
- Evaluations of the patient with cerebral malaria

Measurement of Blood pressure using the Automatic Inflation BP Machine

Procedure

1. Remove tight clothing from the patient's upper arm
2. Place the arm in a position that allows the upper arm to be at the same level with the heart
3. Put the arm through the cuff making sure that the marker is above the brachial artery
4. Pull the end of the cuff and tighten it around the arm making sure that it is not too tight then lock it in place.
5. Connect the cuff to the monitor
6. Set the Inflation control switch to 140 (if a child) or 170 (if a adult).
7. Press the ON/OFF button
8. Wait for the ♥ symbol to appear on the screen then press the start button
9. Make sure the patient does not move the arm or body while the measurement is taking place
10. Note the systolic and diastolic blood pressure and the pulse rate.
11. If there is an error, repeat the process again.

Important

1. Remove tight clothing before taking a measurement so that the measurement is accurate.
2. The cuff should be placed about two centimetres above the elbow and at the same level with the patient's heart.
3. Make sure that the tubing is not bent
4. Measurement should be taken when the patient is not moving because the machine is sensitive to movements.
5. Do not talk while taking the measurement because the machine is sensitive to noise.
6. Wait for 2-3 minutes before repeating a measurement

Measurement of Blood glucose using a glucometer

Supplies needed

1. Advantage glucometer
2. Advantage II glucose test strips
3. Blood lancet
4. Swab

Procedure

1. Gentle squeeze some blood into one of the fingers of the left hand
2. Clean the tip of the finger with the swab
3. Turn the glucometer on and check that it is working well
4. Insert a test strip into the socket with the metallic strips going in first and the blue end facing you
5. Replace the cap on to the tin of strips immediately
6. Insert the lancet with a quick jab into the side of the finger near the tip
7. Squeeze the tip of the finger to obtain a small drop of blood
8. Place the drop of blood on to the edge of the yellow window of the test strip
9. Allow the blood to cover all of the yellow area
10. The glucometer will make a beep and start measuring the glucose level in the sample.
11. Note the reading. If there is an error, repeat the above process again.

Important

1. Do not leave the tin of test strips open otherwise the strips will loose their effectiveness
2. Touch the edge of the yellow window with the drop of blood; do not put the drop on top of the yellow window
3. Cover the entire yellow window with blood otherwise the reading will be incorrect
4. Do not drop the glucometer. If this occurs accidentally, the glucometer has to be calibrated again
5. Calibrate the glucometer before using a new tin of test strips

Evaluation of the patient admitted with cerebral malaria

Day 0 (admission)	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Complete Checklist I	Complete Checklist II	Fill Form 3	Fill Form 3	Fill Form 3
Complete Form 1	Complete Form 2	Fill observations chart	Fill observations chart	Fill observations chart
Do random glucose estimation	Do LP and CSF analysis	Take thick smear for parasite count	Take thick smear for parasite count	Take thick smear for parasite count
Fill observations chart	Take thick smear for parasite count		Take 4 bloodspots on filter paper	
Take thick smear for screening with Field's stain	Collect 3mls (adult) or 1ml (child) into EDTA vacuette for haematological indices			
Take thick smear for parasite count with Giemsa	Collect 2mls (adult) or 1ml (child) into Plain vacuette for serum storage			
Take thin smear for parasite typing	Do urinalysis with Multistix			
Take 4 bloodspots on filter paper	Fill observations chart			
Day 5	**Day 6**	**Day 7 (completes quinine therapy)**	**1 month post-discharge**	**2 months post-discharge**
Fill Form 3	Form 3	Fill Form 3	2nd Neurological assessment	3rd Neurological assessment
Fill observations chart	Fill observations chart	Fill observations chart	Take 4 bloodspots on filter paper	Take 4 bloodspots on filter paper
Take thick smear for parasite count	Take thick smear for parasite count	Administer Information sheet		
		Obtain informed consent		
		Take thick smear for parasite count		
		Take 4 bloodspots on filter paper		
		Complete Form 4 – 1st Neurological assessment		

Appendix III: Protocols for Laboratory evaluations

The procedures contained in this appendix have been mostly taken or adapted to suit the local setting from *Laboratory Practice in Tropical Countries, Part 1* (Cheesbrough 1998).

- Blood smear for malaria
- Parasite count
- Haemogram
- Cerebrospinal fluid analysis
- Urinalysis
- HIV test
- Dried Blood spots
- Storage of serum

Making blood smears (Capillary blood method)

A) Thick smear

1. Get a sterile lancet, swabs of cotton, 70% v/v alcohol, clean slide and disposable pair of gloves.

2. Clean the slide until it is grease-free. Put on the gloves.

3. Cleanse the lobe of the finger (3^{rd} or 2^{nd} fingers) using a swab moistened with 70% v/v alcohol. Allow the area to dry.

4. Use a sterile lancet, prick the lateral aspect of the finger. Wipe the first drop of blood that comes from the site with a clean swab of dry cotton. Squeeze gently to obtain a large drop of blood.

5. Touch the centre of the slide onto the drop of blood. Immediately use a spreader to spread the blood over the slide until it is a thin film that covers about $2/3^{rd}$ of the slide (or 2cm in diameter). The depth of the film should be "thin" enough to allow one to see print if the slide is placed on a book.*

6. Label the slide with the patient's study number, age, ward and Day of management (i.e. Day 0, 1 etc) on the frosted part of the slide. Use a pen with permanent ink (diamond pens that can write on glass were used to label slides that were not frosted).

7. Place the slide horizontally in a safe place and allow to air dry.

B) Thin smear

1. Get the items stated in 1 above including coverslips.

2. Follow steps 1 to 4 above

3. Touch the non-frosted end of the slide onto the drop of blood. Place the slide on a flat surface. Use a coverslip to make a thin smear by touching the coverslip to the drop of blood at an angle between 30^{o} to 60^{o} and sliding it forwards towards the frosted end. The smear should have a tail and head and should cover at least $2/3^{rd}$ of the slide.

4. Follow steps 6 to 7 above.

* It was important to mention this because there was the tendency among nurses to make a thick smear as thick as possible in the belief that this was preferred.

Fixation of thin blood films

1. Get absolute methanol (methyl alcohol), disposable gloves and the dry thin smear to be fixed.
2. Place the slide horizontally on a staining slide rack over the sink.
3. Apply a small drop of methanol onto the thin film.
4. Allow to stand for 1-2 minutes

Staining malaria parasites

A) Field's stain: was used to screen thick smears for malaria parasites.

1. Get Field's stain A and B, clean water, disposable gloves and the dry thick smear to be stained.
2. Dip the slide into the container with Field's stain A until it covers all of the smear. Leave it inside for 5 seconds. Upon taking it out, drain off the excess stain by touching a corner of the slide against the side of the container.
3. Rinse the slide gently with clean water. Drain of the excess water
4. Dip the slide into the container with Field's stain B as above for 3 seconds.
5. Rinse the slide gently with clean water, wipe the back of the slide and stand upright in a draining rack. Allow to air dry or alternatively dry under a light bulb as a second option.

B) Field's stain: was used to stain thin films to identify the species of malaria parasite

1. Get Field's stain A and B, buffered water (pH 7.1-7.2), clean water, disposable gloves and fixed-thin smear for staining.
2. Prepare dilute Field's stain B by mixing 1ml of stain with 4ml of buffered water.
3. Place the smear on a staining rack over the sink.
4. Cover the slide with about ½ ml of diluted Field's stain B
5. Add immediately an equal volume of Field's stain A and mix with the diluted Field's stain B. Leave to stand for 1 minute.
6. Rinse the stain off with clean water. Wipe the back of the slide and place it in a draining rack to air dry.

C) Giemsa staining technique for thick smear (10 minute staining technique).

1. Get Giemsa (Rapid) stain, buffered water (pH 7.1-7.2), disposable gloves and the dry thick smear for staining.

2. Dilute the Giemsa stain by adding 45ml of buffered water to 5 ml of Giemsa stain (1 in 10 dilution). Mix gently.

3. Place the slide in a shallow tray face downwards and pour the diluted stain into the tray. Leave the slide for ten minutes.

4. Rinse the slide with clean water to flush off any excess stain. Wipe the back of the slide and place on a draining rack to air-dry.

Mounting smears with DPX

1. Get DPX mountant, coverslips, disposable gloves and smears to be mounted

2. Using a dropper, place a drop of DPX onto a clean coverslip.

3. Place the slide (smear side downwards) onto the coverslip making sure that there are no bubbles of air in the mountant.

4. Wipe the back of the slide and leave to air-dry

Reporting blood films for malaria parasites

A) Thick film

1. Apply a drop of immersion oil on to the completely dry smear or if mounted onto the coverslip.

2. Carry out a preliminary examination using the 10x and 40x objectives (microscope). Determine the most suitable parts of the film for estimating parasite density and examine the white blood cells for quantity and type.

3. Change to 100x objective and examine the selected part of the film

4. Examine for malaria parasites by looking at 100 high power fields (hpf).

5. Report the approximate number of parasites (trophozoites) according to either the plus sign scheme (for screening purposes only) or the parasite count scheme (for monitoring purposes)

6. If not parasites are seen after looking at 100hpf report the film as "No MPs seen"[†]

[†] It was not routine to repeat smears when parasites were not found.

B) Thin film

1. Apply a drop of oil onto the lower third of the film.
2. Examine the film with 10x then 40x objective. Check staining, morphology and distribution of the cells. Focus on parts of the film in which the RBCs are just touching each other and not overlapping.
3. Identify the species of plasmodia by looking at the ring forms, appearance of PRBCs (size, shape, Schuffner's dots, and number of parasites per cell), and presence of gametocytes and schizonts.
4. Use the 100x objective to confirm the findings in 3 above. Also note the distribution of white blood cells and the shape of the RBCs.

Estimating the Parasite density

A) Plus sign scheme

This scheme is recommended by WHO for estimating the degree of parasitaemia as follows (WHO 1991):

Parasites		Plus sign
1-10	per 100hpf	+
11-100	per 100hpf	++
1-10	in every 1hpf	+++
>10	in every 1hpf	++++

B) Parasite count scheme

This scheme assumes that there are 8000 white blood cells per microlitre (Warhurst and Williams 1996). This standard white blood cell count is used to determine the parasite count as follows:

1. Count the number of malaria parasites per 200 white blood cells[‡].
2. Multiply this number by 40 to obtain the estimated number of malaria parasites per microlitre (mm^3).

[‡] In situations in which the parasitaemia is very high and the number of parasites per hpf are too many to count, one local adaptation developed at Makerere University is to divide each hpf into quarters and count the number of parasites and WBCs per quarter; then multiply the number per quarter in 100hpf by 4.

White blood cell count

Total and differential white blood cell counts were carried out with the Visual method (Dacie and Lewis 1991). This involved the following steps:

1. Make a 1 in 20 dilution of blood by adding 20µL of blood to 0.38 ml of diluting fluid into a plastic tube.
2. Cork the tube and mix thoroughly.
3. Fill the improved Neubauer counting chamber with the mixture using a pipette.
4. View the preparation with 4x objective and count the number of leucocytes.
5. Count the number of cells in 4 squares $1mm^2$ (N) then divide by 4 (N/4) to get the average per $1mm^2$ (equivalent to 0.1µL). The calculate cell count as

cells/L = [number of cells counted divided by volume counted (µL)] x dilution x 10^6

(i.e. N/4 x 1/0.1 x 20 x 10^6 = N x 50 x 10^6/L)

Normal range: Total white cell count is 4,500-10,000/µL in both males and females. Differential is Neutrophils 50-70% (2,500-7,000), Eosinophils 1-3% (100-300), Basophils 0.4-1% (40-100), Lymphocytes 25-35% (1,700-3,500) and Monocytes 4-6% (200-600).

Haemoglobin concentration estimation

Sahli's acid-haematin method using Sahli's tube was used to estimate the blood Hb concentration in g/dL. The procedure was: 1/10 N.HCl was pipetted into Sahl tube to the' 20' mark. 20 µl whole blood was added and mixed. The mixture was left to stand for 10 minutes. Then, diluted with more 1/10 N.HCl until colour matches with the standard. Hb. concentration was read off the scale at the meniscus in g./dl.

Normal range: 12-14 g/dL in children, 14-18 g/dL in adult males, 12-16 g/dL in adult females.

Platelet count

Plates are estimated from a well-prepared thin blood smear. Platelets are counted in 10 microscopic fields using x40 objective. Average number of platelets in the fields is assessed.

Interpretation: The platelets count is reported as:

a) Adequate - if average count is 8-25 in 10 fields

b) Inadequate - if average count is 0-5 in 10 fields.

Blood film

The thin film made to identify malaria parasites was used to report on the blood picture. The size, shape, distribution and texture of red blood cells were examined. Red blood cells were not quantified.

Erythrocyte sedimentation rate

This was estimated using the Westergren method.

1. Use blood that is collected not more than 6 hours ago.

2. Mix the blood sample thoroughly and draw it up into the Westergren tube to the 200 mm mark.

3. Place the tube vertically on the stand. Leave for one hour and read the height of the clear plasma above the upper limit of the column of sedimenting cells. ESR is this measurement (Westergren 1 hr).

Normal range: 4mm/1hr (up to 10) in males and 6mm/1hr (up to 12) in females.

Blood glucose estimation

Blood glucose was measured at the bedside with a portable glucometer (Accu Chek® Advantage II®). Confirmatory measurements were carried out using the colorimetric method. Glucose oxidase (GOD) Peroxidase method uses 4 ml of colour producing reagent (containing the active ingredients (above) plus a chromogen orthodianisidine) mixed with 40 µl serum or plasma. The colour developed is read colorimetrically after 10 minutes and compared to standard solution of glucose treated in the same way. Calculations are made against the standard. Results are recorded as millimoles of glucose/L

Cerebrospinal fluid analysis

Procedures for CSF analysis include:

- Appearance
- Biochemical chemical tests
- White blood cell counts
- Assessing for Micro-organisms

Appearance

1. Normal - clear and colourless
2. Turbid - purulent appearance due to pyogenic meningitis
3. Blood - due to traumatic LP or recent subarachnoid bleeding
4. Xanthochromic - yellowness due to subarachnoid haemorrhage

Biochemical Tests

1. CSF sugar

Preformed using the blood sugar method (Glucose-oxidase). A double amount of specimen is used because of low CSF glucose levels. Results are reported in mmol/L.

Normal values are approximately 2/3 blood glucose levels.

2. CSF protein.

The Trichloroacetic Acid colorimetric method is used (5% w/v).

Protein standards ranging from 10-100mg/dl are prepared. 0.8 ml of a 1/10 dilution of CSF is mixed with 2.4ml of Trichloroacetic acid. The standards are treated in the same way. The turbidity developed after 5 minutes is read colorimetrically. The concentration of protein in the test is CSF is calculated by comparing the test readings with the standard readings. Result multiplied by dilution factor. Results are expressed as mg/dl.

Normal ranges of CSF protein=15 - 45 mg/dl.

3. White blood cell (wbc) count:

WBC count is performed using Neubauer counting chamber. A dilution of 1:5 is made of CSF with diluting fluid. Counting of white cells is done as in white blood cell count using whole blood. Calculation are made taking care of the dilution factor, volume of CSF used and number of cells counted.

wbc/mm^3 = Number counted per mm^3 x volume x dilution.

4. Micro-organisms

The presence of micro-organisms is demonstrated using specific staining procedures.

a) Gram stain for bacteria

b) India blue negative staining for crytococcal meningitis.

c) Ziehl Neelsen stain-for Acid-Fast bacteria

Results are read microscopically

Normal findings: There should be no micro-organisms in a normal CSF

Urinalysis

Bayer® Multistix 10SG reagent strips were used for urinalysis. Specific items measured are: pH, protein, sugar (glucose), ketones, bilirubin, urobilinogen, blood, leucocytes, specific gravity, and nitrite.

HIV test

HIV-1 was measured with ELISA (Welcozyme HIV-1 Recombinant) and Western blot methods.

Dried Blood spots

Four large drops of blood were placed on a square piece of Waterman paper divided at one edged into four strips. After forming dried blood spots (DBS) each piece was placed in a plastic bag and sealed. They were stored in large plastic zipper bags containing silica gel crystals (colour coded type).

Storage of serum

Whole blood was placed in centrifuge tubes (2 ml for adults and 1 ml for children) and centrifuged to separate cells and serum. Serum was then decanted into serum tubes and stored at minus 70°C. At the end of the study the specimens were transport from study hospital in dry ice to UVRI for storage at a central point.

Electrolytes

Electrolytes were measured in the stored sera with Vitalab Selectra E analyzer (vital scientific®.

Normal ranges: Sodium 135-146 mmol/L, Calcium 2-3 mmol/L, Chloride 95-105 mmol/L.

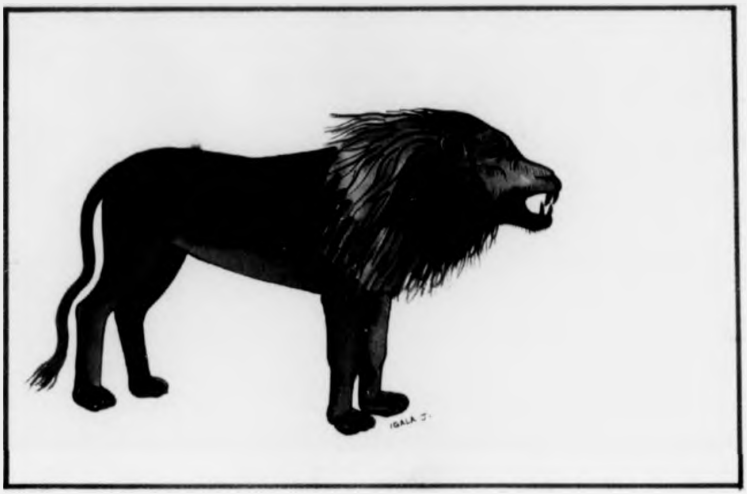
Sickling test

A screening Sickle cell test is performed using Sodium metabisulphite, 2% solution, which is a reducing agent, enhancing the formation of a sickle shape of red cells in a reduced oxygen tension. A drop of blood is mixed with 2 drops 2% of Sodium metabisulphite on a glass slide and covered with a coverslip. The edges of the coverslip are sealed with Vaseline or wax and the preparation is incubated at 37°C for not less than 30 minutes. The preparation is examined microscopically under x10 and x40 objectives. The presence of a number of sickle shaped cells is indicative of Sickle-cell trait or Sickle-cell disease. Longer incubation period may be necessary in case of Sickle-cell. It was not possible to do Haemoglobin Electrophoresis.

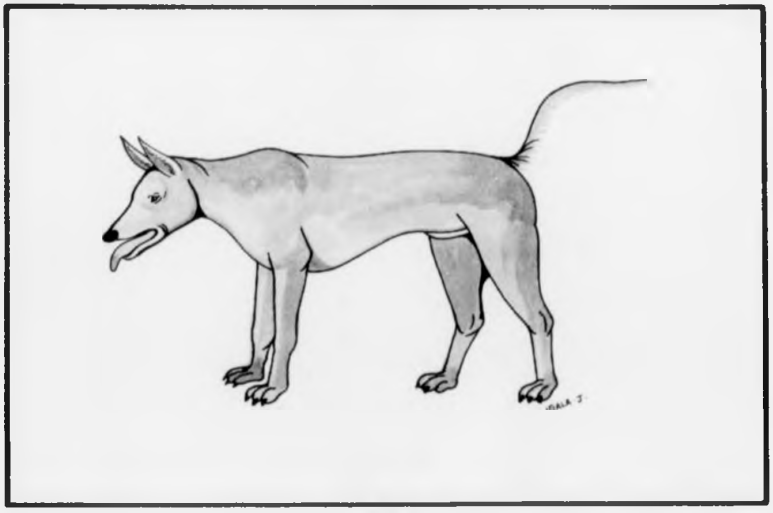
Appendix IV: Pictures used for assessment of adult patients

Sketches of objects that were easy to identify by adult subjects are shown here

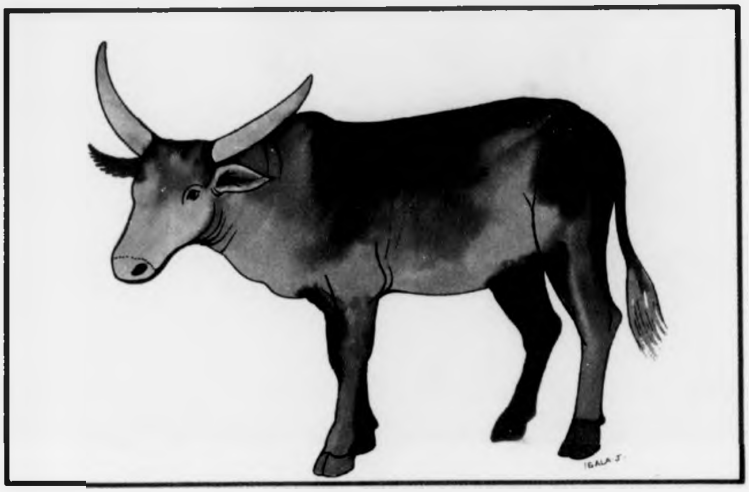
- Lion, Dog, Cow, Goat, 'Matooke' (Bananas), Hen, Chair, Table, Bicycle, Cup.
- Elephant, Cat, Snake, Monkey, Pineapple, Tree, Pot, Car, Hoe, Cup



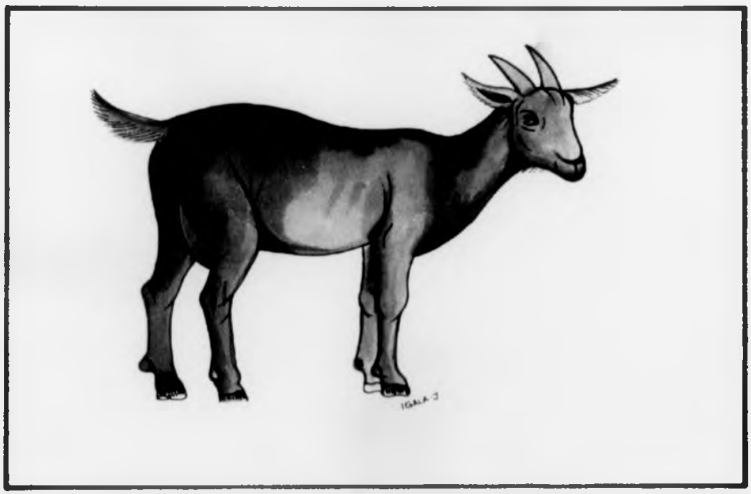
Lion



Dog

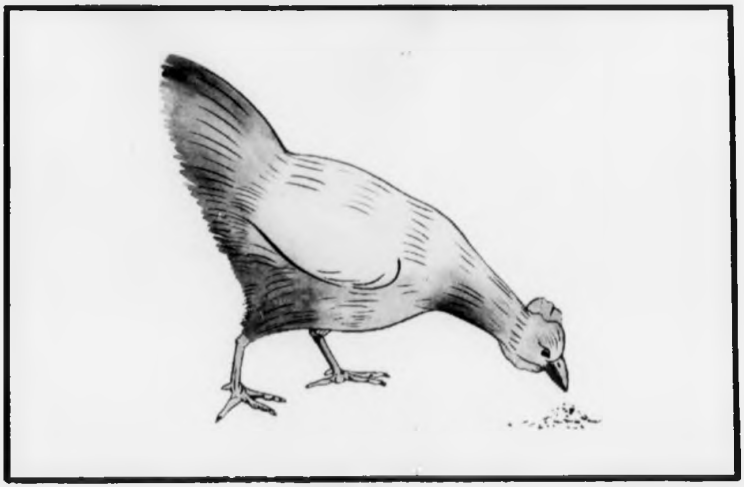


Cow



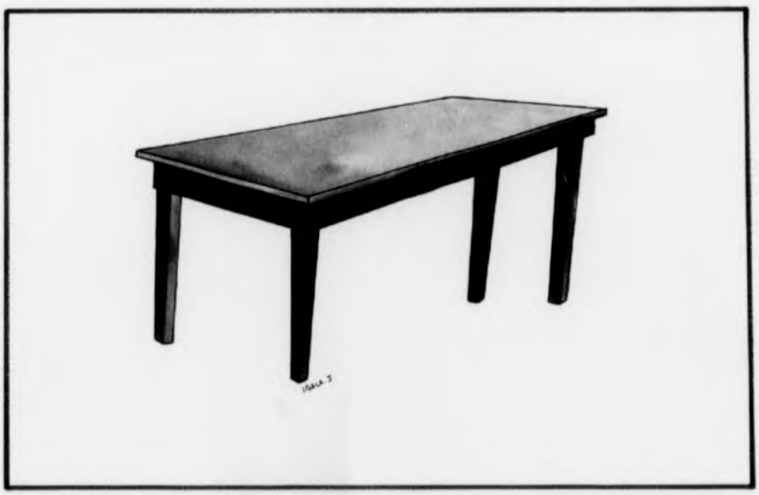
Goat

'Matooke' (Bananas for cooking)

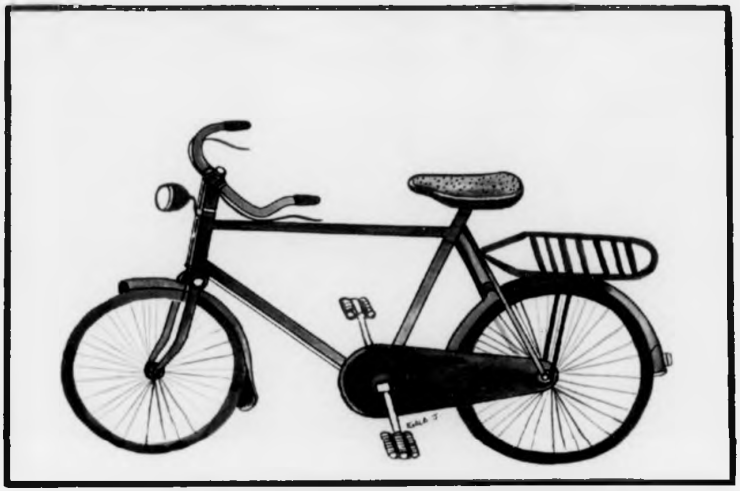


Hen

Chair

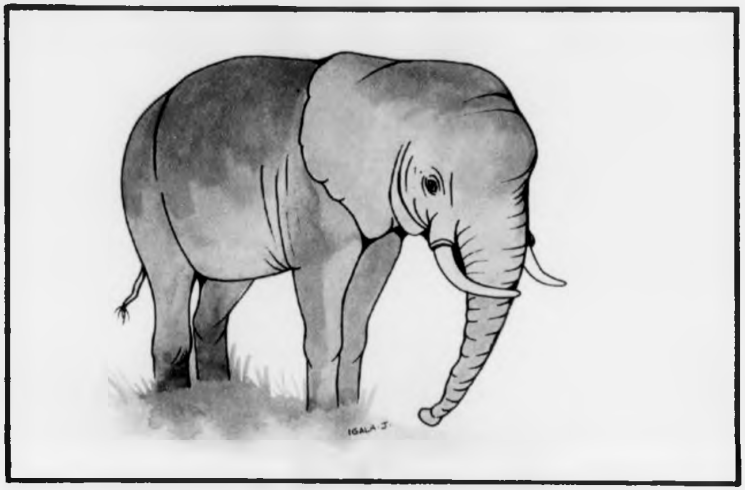


Table

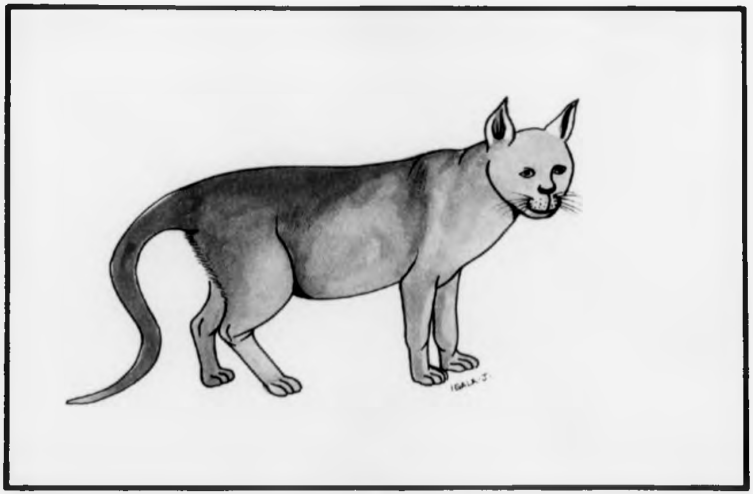


Bicycle

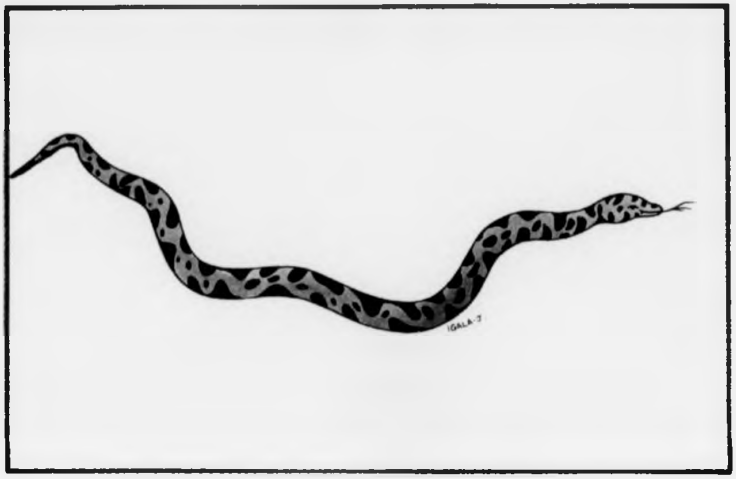
Cup



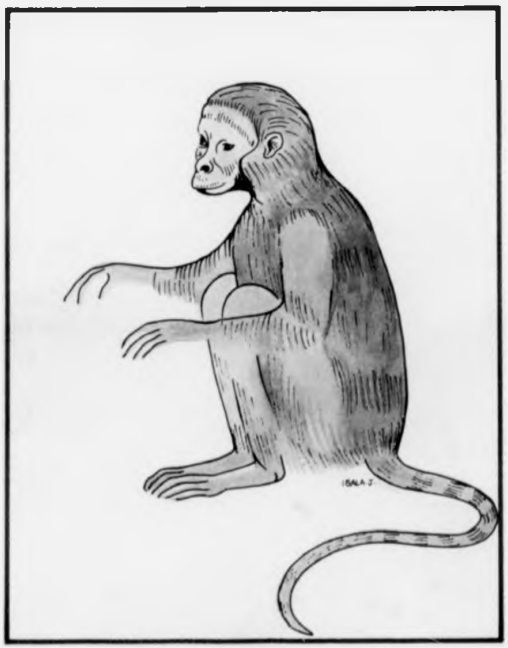
Elephant



Cat



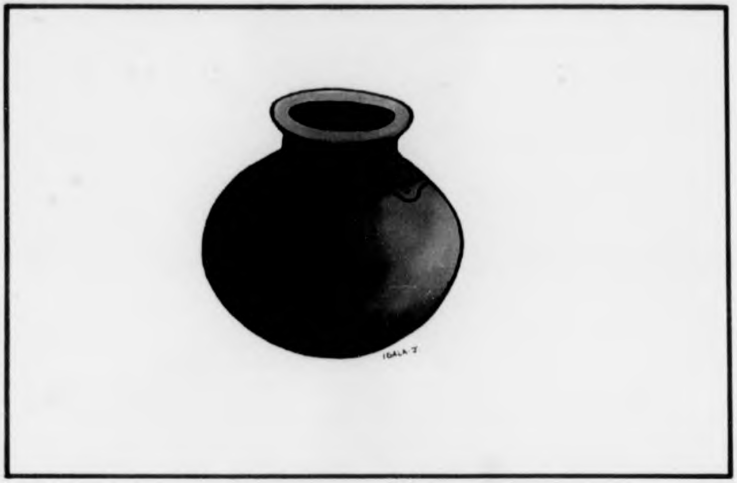
Snake



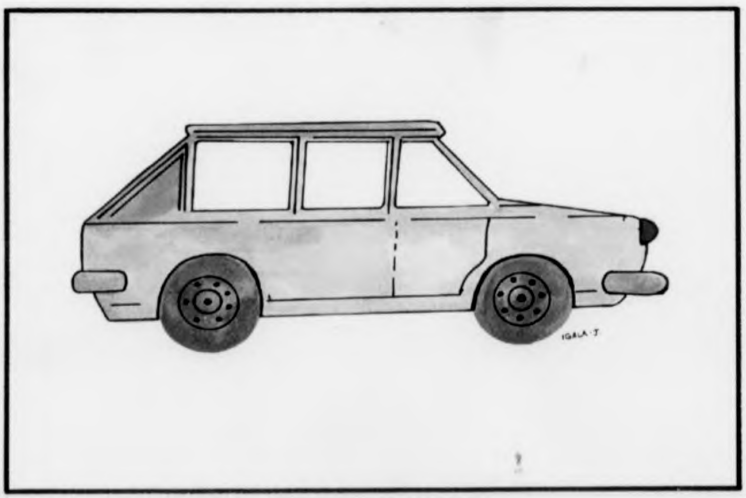
Monkey

Pineapple

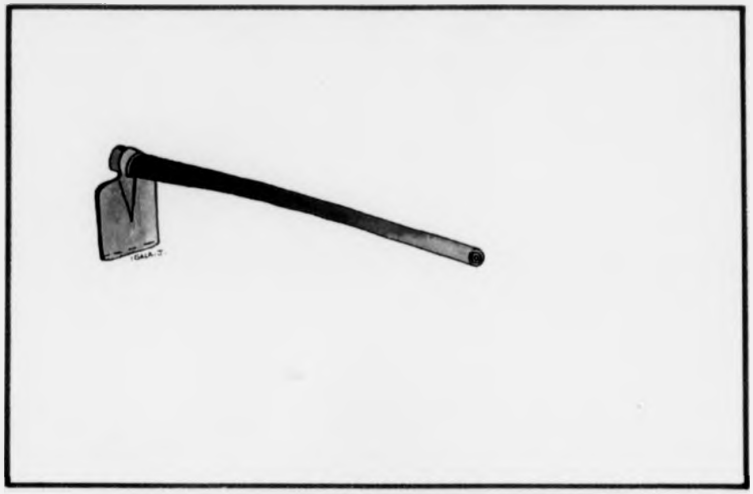
Tree



Pot



Car



Hoe

Appendix V: Tables

- Table A: Table of the odds of mortality
- Table B: Table of the odds of early-onset neurological sequelae
- Table C: Cox regression models for risk factors for mortality
- Table D: Cox regression model for risk factors for late-onset sequelae

Table A: The odds of mortality for explanatory variables used in univariate analyses (N=100)

Variable	No. of observations	No. of deaths	No. of survivors	Odds	Lower 95% CI	Upper 95% CI
Demographic & History information						
Centre (Mbale/Kapchorwa)	70/30	6/4	64/26	0.09/0.15	0.04/0.05	0.21/0.44
Age (less than 10 years/10 and above)	72/28	8/2	64/26	0.13/0.08	0.06/0.02	0.26/0.32
1-4 years	46	6	40	0.15	0.06	0.35
5-9 years	26	2	24	0.08	0.02	0.35
10 and above	28	2	26	0.08	0.02	0.32
Seizures within 24 hours prior to admission						
None	24	5	19	0.26	0.10	0.70
1-3 seizures	43	2	41	0.05	0.01	0.20
4-20 seizures	33	3	30	0.10	0.03	0.33
Quinine given prior to admission (No/Yes)	62/38	9/1	53/37	0.17/0.03	0.08/0.00	0.34/0.20
Previous medical admission to hospital (No/Yes)	86/14	9/1	77/13	0.12/0.08	0.06/0.01	0.23/0.59
Clinical examination on admission						
Able to localise painful stimuli at Level 1 (No/Yes)	52/48	7/3	45/45	0.16/0.07	0.07/0.02	0.34/0.21
Coma depth measured on Blantyre Coma Scale						
0-2	31	4	27	0.15	0.05	0.42
3-5	10	0	10	0.00	-	-
No Score/Missing info	59	6	53	0.11	0.05	0.26
Coma depth measured on Glasgow Coma Scale						
3-8	19	2	17	0.12	0.03	
9-12	22	0	22	0.00	-	-
13-15	5	0	5	0.00	-	-
No Score/Missing info	54	8	46	0.17	0.08	0.37
Body temperature						
35.0-38.5 °C	63	6	57	0.11	0.05	0.24
38.6-39.4 °C	28	2	26	0.08	0.02	0.32
39.6-42.0 °C	9	2	7	0.29	0.06	1.38
Moderate – severe anaemia (No/Yes)	51/49	6/4	45/45	0.13/0.09	0.06/0.03	0.31/0.25
Clinical signs of jaundice (No/Yes)	86/14	10/0	76/14	0.13/0.00	0.07/0.00	0.25/0.00
Clinical signs of moderate – severe dehydration (No/Yes)	92/8	9/1	83/7	0.11/0.14	0.05/0.02	0.21/1.16

Table continued overleaf

Table A continued

Variable	No. of observations	No. of deaths	No. of survivors	Odds	Lower 95% CI	Upper 95% CI
Shock (Unlikely/Likely)	95/5	10/0	85/5	0.12/0.00	0.06/0.00	0.23/0.00
Presence of extra heart sounds						
No	72	4	68	0.06	0.02	0.16
Yes	13	1	12	0.08	0.01	0.64
Missing	15	5	10	0.50	0.17	1.46
Pulse pressure						
20-39 mmHg	14	1	13	0.08	0.01	0.59
40-79 mmHg	17	1	16	0.06	0.01	0.47
Missing info	69	8	61	0.13	0.06	0.27
Respiratory abnormality (No/Yes)	58/42	6/4	52/38	0.12/0.11	0.05/0.04	0.27/0.29
Respiratory distress (Not likely/Likely)	95/5	10/0	85/5	0.12/0.00	0.06/-	0.23/-
In-hospital non-laboratory information						
First episode of witnessed seizures (none/any number)		9/1	45/45	0.20/0.02	0.10/0.00	0.41/0.16
None	54	9	45	0.20	0.10	0.41
1-3 seizures	31	1	30	0.03	0.00	0.24
4-20 seizures	15	0	15	0.00	-	-
Seizure stoppage time						
1 day	24	1	23	0.04	0.01	0.32
2 days	12	0	12	0.00	-	-
3 48 days	10	0	10	0.00	-	-
No seizures	54	9	45	0.20	0.10	0.41
Total seizure stoppage time						
1 days	23	2	21			
2 days	25	0	25			
3-48 days	33	2	31			
No seizures	19	6	13			
Duration of unrousable coma						
Not in unrousable coma on admission	26	0	26	0.00	-	-
For less than 48 hours	35	2	33	0.06	0.01	0.25
For 48 hours or more	25	0	25	0.00	-	-
Missing info	14	8	6	1.33	0.46	3.84
Coma recovery time						
1-2 days	25	1	24	0.04	0.01	0.31
3-4 days	33	0	33	0.00	-	-
5 and above	14	0	14	0.00	-	-
Missing Info	28	9	19	0.47	0.21	1.05
Total coma recovery time						
1-2 days	31	5	26	0.19	0.07	
3-4 days	28	0	28	0.00	-	-
5 and above	30	0	30	0.00	-	-
Missing info	11	5	6	0.83	0.25	2.73

Table continued overleaf

Table A continued

Variable	No. of observations	No. of deaths	No. of survivors	Odds	Lower 95% CI	Upper 95% CI
Fever clearance time						
1 day	31	5	26	0.19	0.07	0.50
2-3 days	40	4	36	0.11	0.04	0.31
4-9 days	25	1	24	0.04	0.00	0.31
Missing info	4	0	4	0.00	-	-
Total fever clearance time						
1-4 days	39	7	32	0.22	0.10	0.50
5-6 days	32	2	30	0.07	0.02	0.28
7-20 days	29	1	28	0.04	0.00	0.26
Quinine loading dose prescribed on admission						
No	78	6	72	0.08	0.04	0.19
Yes	5	1	4	0.25	0.03	2.24
Missing	17	3	14	0.21	0.06	0.75
Total amount of quinine given on Day 0						
225 – 569 mg	40	4	36	0.11	0.04	0.31
570 – 1800 mg	41	2	39	0.05	0.01	0.21
Missing info	19	4	15	0.27	0.09	0.80
Duration of hospital stay						
Less than 6 days	36	10	26	0.38	0.19	0.80
6 to 8 days	50	0	45	0.00	-	-
More than 8 days	14	0	14	0.00	-	-
Laboratory based information						
Random blood glucose on admission (>2.2/≤2.2mmol/L)	92/8	10/0	82/8	0.12/0.00	0.06/-	0.24/-
Less than 5 mmol/L	22	2	20	0.10	0.02	0.43
5 – 6.9 mmol/L	26	1	25	0.04	0.01	0.30
7 and above	22	1	21	0.05	0.01	0.35
Missing info	30	6	24	0.25	0.10	0.61
Parasite count	100					
50,000 parasites/μL and below	52	2	50	0.04	0.01	0.16
> 50,000 parasites/μL	33	5	28	0.17	0.07	0.46
Missing info	15	3	12	0.25	0.07	0.89
Parasite clearance time						
1 day	35	2	33	0.06	0.01	0.25
2 days	35	4	31	0.12	0.05	0.37
3-4 days	12	0	12	0.00	-	-
Missing info	18	4	14	0.29	0.09	0.87
Haemoglobin concentration						
3.0-9.9 g/dL	38	4	34	0.12	0.04	0.33
10.0-15.0 g/dL	30	2	28	0.07	0.02	0.30
Missing info	32	4	28	0.14	0.05	0.41

Table continued overleaf

Table A continued

Variable	No. of observations	No. of deaths	No. of survivors	Odds	Lower 95% CI	Upper 95% CI
HIV infection						
No	32	4	28	0.14	0.05	0.41
Yes	5	0	5	0.00	-	-
Missing	63	6	57	0.11	0.05	0.24
Serum Sodium concentration						
<135 mmol/L	33	4	29	0.14	0.05	0.39
135-146 mmol/L	20	1	19	0.05	0.01	0.39
>146 mmol/L	8	1	7	0.14	0.02	1.16
Missing info	39	4	35	0.11	0.04	0.32
Serum Calcium concentration						
<2 mmol/L	15	0	15	0.00	-	-
2-3 mmol/L	12	1	11	0.09	0.01	0.70
>3 mmol/L	26	3	23	0.13	0.04	0.43
Missing info	47	6	41	0.15	0.06	0.34
Serum Chloride concentration						
<95 mmol/L	4	0	4	0.00	-	-
95-105 mmol/L	10	2	8	0.25	0.05	1.18
>105 mmol/L	36	2	34	0.06	0.01	0.24
Missing info	50	6	44	0.14	0.06	0.32
White blood cell count						
2000-4700 cells/L	25	2	23	0.09	0.02	0.37
4701-6700 cells/L	26	1	25	0.04	0.01	0.30
6701-27000 cells/L	25	3	22	0.14	0.04	0.46
Missing info	24	4	20	0.20	0.07	0.59

Table B: The odds of early-onset neurological deficits for explanatory variables used in univariate analyses (N=90)

Variable	No. of observations	No. with deficits	No. without deficits	Odds	Lower 95% CI	Upper 95% CI
Demographic & History information						
Centre (Mbale/Kapchorwa)	64/26	17/6	47/20	0.36/0.30	0.21/0.12	0.63/0.75
Age (less than 10 years/10 and above)	64/26	17/6	47/20	0.36/0.30	0.21/0.12	0.63/0.75
1-4 years	40	8	32	0.25	0.11	0.54
5-9 years	24	9	15	0.60	0.26	1.37
10 and above	26	6	20	0.30	0.12	0.75
Seizures within 24 hours prior to admission (None/Any number)	19/71	2/21	17/50	0.12/0.42	0.03/0.25	0.51/0.70
None	19	2	17	0.12	0.03	0.51
1-3 seizures	41	11	30	0.37	0.18	0.73
4-20 seizures	30	10	20	0.50	0.23	1.07
Quinine given prior to admission (No/Yes)	53/37	9/14	44/23	0.20/0.61	0.10/0.31	0.42/1.18
Previous medical admission to hospital (No/Yes)	77/13	18/5	59/8	0.31/0.63	0.18/0.20	0.52/1.91
Clinical examination on admission						
Able to localise painful stimuli at Level 2 (No/Yes)	65/25	17/6	48/19	0.35/0.31	0.20/0.12	0.61/0.79
Coma depth measured on Blantyre Coma Scale (cases aged 5 yrs and below)						
0-2	26	6	20	0.30	0.12	0.75
3-5	10	3	7	0.43	0.11	1.66
No Score/Missing info	6	0	6	-	-	-
Coma depth measured on Glasgow Coma Scale (cases aged over 5 years)						
3-8	17	6	11	0.54	0.20	1.47
9-12	22	6	16	0.38	0.15	0.96
13-15	5	0	5	-	-	-
No Score/Missing info	4	2	2	1.00	0.14	7.10
Body temperature						
35.0-38.5 °C	57	17	40	0.43	0.24	0.75
38.6-39.4 °C	26	5	21	0.24	0.09	0.63
39.5-42.0 °C	7	1	6	0.17	0.02	1.38

Table continued overleaf

Table B continued

Variable	No. of observations	No. with deficits	No. without deficits	Odds	Lower 95% CI	Upper 95% CI
Moderate – severe anaemia (No/Yes)	45/45	12/11	33/34	0.36/0.32	0.19/0.16	0.70/0.64
Clinical signs of jaundice (No/Yes)	76/14	19/4	57/10	0.33/0.40	0.20/0.13	0.56/1.28
Clinical signs of moderate – severe dehydration (No/Yes)	83/7	22/1	61/6	0.36/0.17	0.22/0.02	0.59/1.38
Shock (Unlikely/Likely)	85/5	23/0	62/5	0.37/-	0.23/-	0.60/-
Presence of extra heart sounds						
No	59	22	37	0.60	0.35	1.01
Yes	9	1	8	0.13	0.02	1.00
Missing	3	0	3	-	-	-
Pulse pressure						
20-39 mmHg	13	2	11	0.18	0.04	0.82
40-79 mmHg	16	3	13	0.23	0.07	0.81
Missing info	61	18	43	0.42	0.24	0.73
Respiratory abnormality (No/Yes)	52/38	14/9	38/29	0.37/0.31	0.20/0.15	0.68/0.66
Respiratory distress (Not likely/Likely)	85/5	22/1	63/4	0.35/0.25	0.21/0.03	0.57/2.24
Presence of Organomegaly (No/Yes)	57/33	10/13	47/20	0.21/0.65	0.11/0.32	0.42/1.31
Enlarged spleen (No/Yes)	72/18	15/8	57/10	0.26/0.80	0.15/0.32	0.46/2.03
Enlarged liver (No/Yes)	72/18	18/5	54/13	0.33/0.38	0.20/0.14	0.57/1.08
In-hospital non-laboratory information						
First episode of witnessed seizures (none/any number)	45/45	11/12	34/33	0.32/0.36	0.16/0.19	0.64/0.70
None	45	11	34	0.32	0.16	0.64
1-3 seizures	30	5	25	0.20	0.08	0.52
4-20 seizures	15	7	8	0.88	0.32	2.41
Seizure stoppage time						
1-2 days	35	8	27	0.30	0.13	0.65
3-48 days	10	4	6	0.67	0.19	2.36
Total seizure stoppage time						
1-2 days	46	9	37	0.24	0.12	0.50
3-48 days	31	11	20	0.55	0.26	1.15
Duration of unrousable coma						
Not in unrousable coma on admission	26	6	20	0.30	0.12	0.75
For less than 48 hours	33	8	25	0.32	0.14	0.71
For 48 hours or more	25	9	16	0.56	0.25	1.27
Missing info	6	0	6	-	-	-

Table continued overleaf

Table B continued

Variable	No. of observations	No. with deficits	No. without deficits	Odds	Lower 95% CI	Upper 95% CI
Coma recovery time						
1-2 days	24	4	20	0.20	0.07	0.59
3-4 days	33	9	24	0.38	0.17	0.81
5 and above	14	8	6	1.33	0.46	3.84
Missing Info	19	2	17	0.12	0.03	0.51
Total coma recovery time						
1-2 days	26	3	23	0.13	0.04	0.43
3-4 days	28	5	23	0.22	0.08	0.57
5 and above	30	15	15	1.00	0.49	2.05
Missing info	6	0	6	-	-	-
Fever clearance time						
1 day	26	9	17	0.53	0.24	1.19
2-3 days	36	6	30	0.20	0.08	0.48
4-9 days	24	6	18	0.33	0.13	0.84
Missing info	4	2	2	1.00	0.14	7.10
Total fever clearance time						
1-4 days	32	12	20	0.60	0.29	1.23
5-6 days	30	5	25	0.20	0.08	0.52
7-20 days	28	6	22	0.27	0.11	0.67
Quinine loading dose prescribed on admission						
No	72	22	50	0.44	0.26	0.73
Yes	4	1	3	0.33	0.03	3.20
Missing	14	0	14	0.00	-	-
Dose of quinine given on Day 0						
3-8.9 mg/kg	7	3	4	0.75	0.17	3.35
9.0-10.9 mg/kg	19	7	12	0.58	0.23	1.48
11.0-20.9 mg/kg	18	5	13	0.38	0.14	1.08
Missing info	46	8	38	0.21	0.10	0.45
Duration of hospital stay						
Less than 6 days	26	4	22	0.18	0.06	0.53
6 to 8 days	50	12	38	0.32	0.17	0.60
More than 8 days	14	7	7	1.00	0.35	2.85
Laboratory based information						
Random blood glucose on admission (>2.2/≤2.2mmol/L)	82/8	21/2	61/6	0.34/0.33	0.21/0.07	0.57/1.65
Less than 5 mmol/L	20	6	14	0.43	0.16	1.12
5 – 6.9 mmol/L	25	5	20	0.25	0.09	0.67
7 and above	21	9	12	0.75	0.32	1.78
Missing info	24	3	21	0.14	0.04	0.48
Parasite count						
50,000 parasites/μL and below	50	12	38	0.32	0.17	0.60
> 50,000 parasites/μL	28	8	20	0.40	0.18	0.91
Missing info	12	3	9	0.33	0.09	1.23

Table continued overleaf

Table B continued

Variable	No. of observations	No. with deficits	No. without deficits	Odds	Lower 95% CI	Upper 95% CI
Parasite clearance time						
1 day	33	11	22	0.50	0.24	1.03
2 days	31	5	26	0.19	0.07	0.50
3-4 days	12	4	8	0.50	0.15	1.66
Missing info	14	3	11	0.27	0.08	0.98
Haemoglobin concentration						
3.0-9.9 g/dL	34	9	25	0.36	0.17	0.77
10.0-15.0 g/dL	28	10	18	0.55	0.26	1.20
Missing info	28	4	24	0.17	0.06	0.48
HIV infection						
No	28	4	24	0.17	0.06	0.48
Yes	5	1	4	0.25	0.03	2.24
Missing		18	39	0.46	0.26	0.81
Serum Sodium concentration						
<135 mmol/L	29	6	23	0.26	0.11	0.64
135-146 mmol/L	19	2	17	0.12	0.03	0.51
>146 mmol/L	7	2	5	0.40	0.08	2.06
Missing info	35	13	22	0.59	0.30	1.17
Serum Calcium concentration						
<2 mmol/L	15	2	13	0.15	0.03	0.68
2-3 mmol/L	11	1	10	0.10	0.01	0.78
>3 mmol/L	23	5	18	0.28	0.10	0.74
Missing info	41	15	26	0.58	0.31	1.09
Serum Chloride concentration						
<95 mmol/L	4	1	3	0.33	0.03	3.20
95-105 mmol/L	8	1	7	0.14	0.02	1.16
>105 mmol/L	34	6	28	0.21	0.09	0.52
Missing info	44	15	29	0.52	0.28	0.96
White blood cell count						
2000-4700 cells/L	23	9	14	0.64	0.28	1.49
4701-6700 cells/L	25	2	23	0.09	0.02	0.37
6701-27000 cells/L	22	7	15	0.47	0.19	1.14
Missing info	20	5	15	0.33	0.12	0.92

Table C: Cox regression models of risk factors for mortality identified by logistic regression (compare with Table 5.3)

Risk factor	HR	P-value*	Lower 95% CI	Upper 95% CI
Model 1 (N= 100)				
Aged ten years and above	0.60	0.521	0.13	2.87
Managed in Kapchorwa hospital	1.48	0.549	0.41	5.36
Quinine given prior to admission	0.17	0.093	0.02	1.35
Had seizures while on the ward	0.13	0.051	0.02	1.01
Model 2 (N=58)†				
Aged ten years and above	0.41	0.333	0.07	2.48
Managed in Kapchorwa hospital	2.52	0.237	0.54	11.72
Quinine given prior to admission	0.15	0.081	0.02	1.27
Had seizures while on the ward	0.08	0.019	0.01	0.67
Model 3 (N=58)‡				
Aged ten years and above	0.32	0.231	0.05	2.05
Managed in Kapchorwa hospital	2.51	0.242	0.54	11.70
Quinine given prior to admission	0.17	0.104	0.02	1.44
Had seizures while on the ward	0.10	0.032	0.01	0.82
Parasite count				
≤ 50,000 parasites/μL	1			
> 50,000 parasites/μL	4.39	0.085	0.81	23.62
Missing info	4.54	0.108	0.72	28.67

* Calculated from the Wald test
† Variables from Model 1 but restricted to *definite* cases
‡ Model fitted by adjusting for case definition at the onset

Table D: Cox regression models of risk factors for late-onset neurological sequelae (compare with Table 5.10)*

Risk factor	HR	P value	Lower 95% CI	Upper 95% CI
Model 1b (n=90)†				
Aged over ten years	3.51	0.093	0.81	15.17
Admitted to hospital before	0.39	0.414(C)	0.04	3.77
Body temperature		(C)		
35.0-38.5 °C	1			
38.6-39.4 °C	0.83	0.795	0.20	3.47
39.5-42.0 °C	3.77	0.349	0.23	60.72
Fever clearance time				
1 day	1			
2-3 days	0.76	0.737	0.16	3.68
4-9 days	18.91	0.014	1.83	195.48
Seizure stoppage time				
1-2 days	1			
3-48 days	3.63	0.269	0.37	35.81
No recorded seizures	8.27	0.071	0.84	81.74
Total coma recovery time		(C)		
1-2 days	1			
3-4 days	2.28	0.451	2.67	19.51
5 and above	2.40	0.381	0.34	17.11
Was hypoglycaemic on admission	5.77	0.377 (C)	0.12	282.80
Had deficits at discharge	9.89	0.006	1.94	50.45
Model 2b (n=90)‡				
Aged over ten years	1.98	0.264	0.60	6.61
Fever clearance time				
1 day	1			
2-3 days	0.81	0.757	0.21	3.08
4-9 days	5.50	0.066	0.90	33.77
Seizure stoppage time				
1-2 days	1			
3-48 days	4.88	0.079	0.83	28.56
Missing	5.27	0.031	1.16	23.92
Had deficits at discharge	7.37	0.004	1.90	28.62

* Adjusted for centre and using age as two categories

† Includes clinically significant variables (marked as C); Global test of proportional hazards (PH) assumption, chi^2 (6.69), df (13) and P value = 0.917. The category of body temperature 38.6-39.4 °C violated the PH assumption.

‡ Does not include clinically significant variables as in Model 1b.; Global test of proportional hazards (PH) assumption, chi^2 (1.64), df (7) and P value = 0.977. None of the categories violated the PH assumption

Appendix VI: Figures

- **Figure A: Logistic regression diagnostic plot assessing the goodness-of-fit of Model 1 in Table 5.3.**
- **Figure B: Logistic regression diagnostic plot assessing the goodness-of-fit of Model 2 in Table 5.3.**
- **Figure C: Logistic regression diagnostic plot assessing the goodness-of-fit of Model 3 in Table 5.3.**
- **Figure D: Logistic regression diagnostic plot assessing the goodness-of-fit of Model 1a in Table 5.6.**
- **Figure E: Logistic regression diagnostic plot assessing the goodness-of-fit of Model 2a in Table 5.7.**

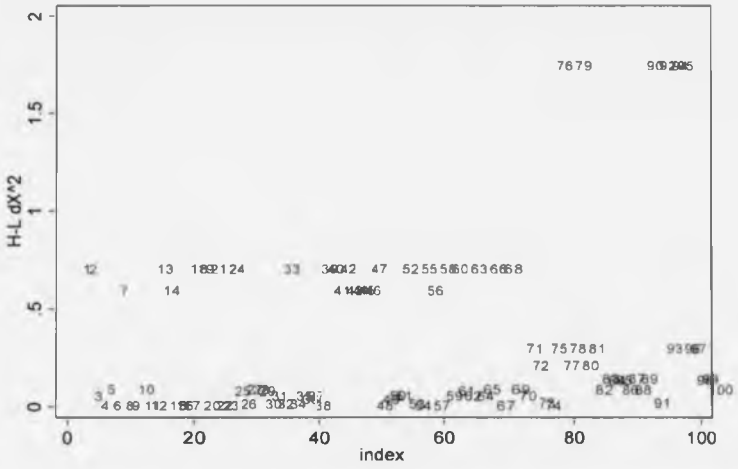


Figure A: Logistic regression diagnostic plot of Hosmer and Lemeshow influence (H-L dx2) for 100 cases of cerebral malaria (represented as index numbers from 1 to 100) assessing the goodness-of-fit of Model 1 in Table 5.3.

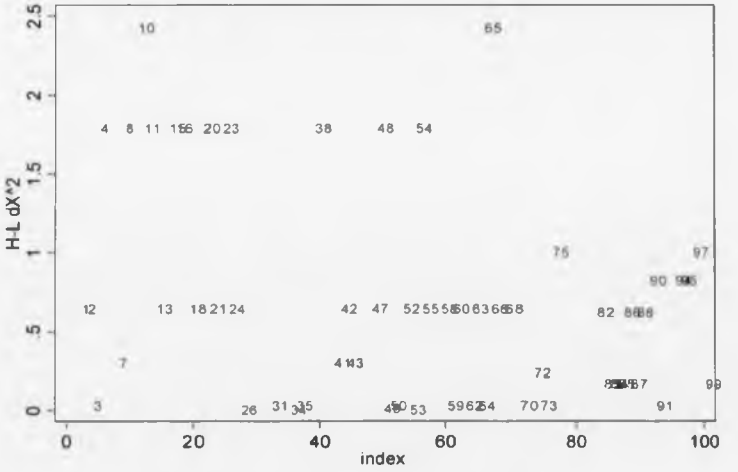


Figure B: Logistic regression diagnostic plot of Hosmer and Lemeshow influence (H-L dx2) for 58 definite cases of cerebral malaria (represented as index numbers between 1 to 100) assessing the goodness-of-fit of Model 2 in Table 5.3.

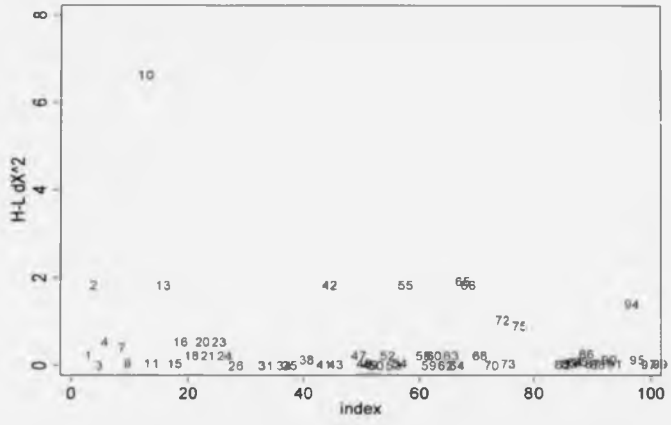


Figure C: Logistic regression diagnostic plot of Hosmer and Lemeshow influence (H-L dx2) for 58 definite cases of cerebral malaria (represented as index numbers between 1 to 100) assessing the goodness-of-fit of Model 3 in Table 5.3.

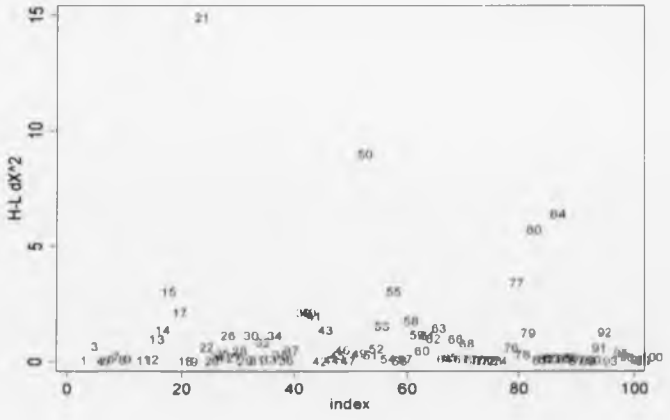


Figure D: Logistic regression diagnostic plot of Hosmer and Lemeshow influence (H-L dx2) for 90 survivors of cerebral malaria (represented as index numbers between 1 to 100) assessing the goodness-of-fit of Model 1a in Table 5.6

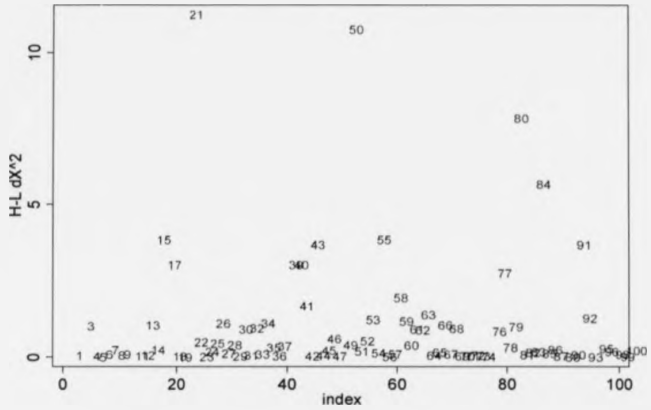


Figure E: Logistic regression diagnostic plot of Hosmer and Lemeshow influence (H-L dx2) for 90 survivors of cerebral malaria (represented as index numbers between 1 to 100) assessing the goodness-of-fit of Model 2a in Table 5.7

Appendix VI: Miscellaneous items

The following items can be found in this appendix:

- Newspaper cuttings of warnings on the heavy rains in 2002
- Findings of the exercise to validate the diagnoses of cerebral malaria recorded in the inpatient registers of patients admitted between 1st January 1999 and 31st December 2000.
- Poster on guidelines for the 'Management of the Patient with severe malaria' for use at hospitals in Uganda that I played a role in developing for the Ministry of Health, Uganda and the Malaria Consortium, East Africa Office.

Clips from *The New Vision* newspaper warning the public of the impending heavy rains during the rainy season, September-December 2002.

Ready for El Nino?

WATER EVERYWHERE: A night time downpour left this street in Bwaise flooded. The water even entered into homes, shops and other businesses

By Andrew Ndawula Kaleema

capacity to clear the channel of debris before the next heavy downpour brings in a

green reserves, have all been built up, critically reducing the city's capacity to absorb

Just Asking

Belinda Namutebi, the host of *Belinda's Lounge* on Sanyu FM every weekday morning and *The Hill Replay* on Saturdays, is as charming on the phone as she is on air. We called her up to bother her with five clever questions.

Q: Did Census guys count you to find out how many Belindas there are?
A: No. They came when I wasn't home. I think it was a waste of our time. They should have sent a questionnaire and then come and collect it.

Govt issues El-Nino alert

By Alfred Wasike

THE Government has called for a national alert against the destructive El-Nino rains that have killed people, displaced others and destroyed property in Europe and Asia and are expected to hit Uganda from mid this month through to next year.

District authorities and Local Councils have been instructed to immediately form El-Nino task forces to prepare households against the effects of the rains which meteorologists predict will be heavy with violent thunderbolts and lightning.

The task forces, to be coordinated by the Ministry of Disaster Preparedness & Refugees, are to help combat expected epidemics, evacuate stranded victims and sensitise the public on the use of thunderbolt conductors

especially in Universal Primary Education schools and institutions like hospitals.

Issuing the national alert, the lands state minister Bugisha Isoke, yesterday told a press briefing moderated by information minister, Basoga Nsadhu: "We are not taking chances. We learnt better lessons from the destruction in 1997/98. The task forces must be formed immediately.

"It will be an abnormally prolonged rainy season. We shall experience floods and are also likely to be hit by epidemics like cholera and diarrhoea," Isoke said.

He said the Government had organised an emergency inter-ministerial workshop in Kisoro to "review the effects of the 1997/98 El-Nino and advise accordingly on the coming rains".

Museveni okay with Police — Katumba

LISTEN: Katumba addresses officers at Kaliziro in Rakai after touring their barracks

Eddie Sadigha

THE Inspector General of Police, Maj Gen. Katumba Wamala, has said there was no rift between the President and the Police force, adding that Museveni's recent remarks about them was a mere challenge to work harder, reports

Katumba was responding to complaints from residents of Kyotera town in Rakai about the President's remarks concerning the force yet according to them he (Katumba) had made big reforms that Museveni should have recognised.

"There are no contradictions between the President and the Police. There are many ways of encouraging one to work harder. Do not expect praises all the time," Katumba said.

The IGP, who was on a two-days tour of Rakai, said the President's comments were a challenge to the force.

"His comments are a challenge to us as a Police force. He is telling us to wake up and perform better.

"He is telling us that if we have criminals in the force, we must remove them and yes we have criminals," Katumba said.

He cited the case concerning the policewoman who was recently arrested for supplying guns to criminals as well as that of the Special Police Constable who was last week killed during a robbery on Kanemeero road in Rakai district.

IN BRIEF

Defiler jailed

KAMPALA — Nakawa Court yesterday convicted a 20-year-old man for attempting to defile a 12-year-old girl and sentenced him to 10 years imprisonment. The Chief Magistrate, Margaret Mutebi, convicted a casual labourer, Amos Ongei Mungu, of Mutungo in Nakawa Division after prosecution proved him guilty of the offence of attempted defilement.

Case flops

KAMPALA — Nakawa Court has dismissed a case involving a man charged with possession of immature fish. Godfrey Semuuza, 30, of Ndeeba, appeared before the Chief Magistrate, Margaret Mutebi and denied the charge. Prosecution alleged that the accused and others still at large committed the crime on April 12.

Man fined

KAMPALA — Buganda Road Court has fined a builder shs40,000 for being in possession of a pistol without a certificate. Magistrate Vincent Mugabo told Ronald Seku, 36, a resident of Kazo in Kawempe, to pay the fine after prosecution proven beyond reasonable doubt that he had

The findings of an exercise to validate the diagnoses of cerebral malaria recorded in the inpatient registers of patients admitted to Kabale hospital between 1st January 1999 and 31st December 2000.

After noticing the scarcity of patients with features of cerebral malaria, an exercise to verify the recorded diagnoses of cerebral malaria in the inpatient register was embarked upon. To do this, a scoring system that ranked the quality of the diagnosis was devised and it incorporated information from the history, clinical examination and laboratory. I called this the "cerebral malaria diagnosis" scale and its components are shown in Table E below. A *definite* case of cerebral malaria would score between 11 and 16 (the maximum score on the scale). The higher the score the more aspects of the research definition that were met. A *probable* case of cerebral malaria (i.e. practical definition), would score between 5 and 10 and anything between 0 and 4 was unlikely to be cerebral malaria. This scoring system enabled one to examine the retrospective records and come to some estimate of the accuracy of a diagnosis of CM even if the records are scanty. This "cerebral malaria diagnosis" scale had been tried on a random selection of cases admitted to New Mulago hospital. Of thirty-five cases with a final diagnosis of cerebral malaria admitted in 1999 (selected to coincide with one of the years of the epidemic of malaria in the highland areas of Uganda), 4 cases (11%) scored 11-12 (i.e. DCM) and 28 cases (80%) scored 5-10 (i.e. PCM); and 3 cases scored 3-4 (i.e. unlikely to be CM). The scale was used to determine how many of the patients admitted to Kabale with a final diagnosis of cerebral malaria in their notes could meet the requirements on the scale. The years used are 1999 and 2000 because that was the time when an epidemic of malaria took place there. This exercise showed, see Table F, that few patients whose files I was able to examine with a diagnosis of cerebral malaria (or severe malaria) met the requirements on the scale. This was an indication that cerebral malaria even during the time when there was an epidemic of malaria in the region was being over diagnosed.

Table E: The cerebral malaria diagnosis scale; a scoring system for the retrospective diagnosis of cerebral malaria,

Characteristic	Components	Score	D_{max}*	D_{min}†	P_{min}‡	N_{min}§
A. Symptoms provided in history	1. Loss of consciousness	1	1	1	1	
	2. Afebrile convulsions (<10yrs)	1				
	3. Convulsions (>10yrs)	1	1			
	4. Confusion (>10yrs)	1				
	5. None	0				0
B. Level of consciousness (sign)	1. Unrousable coma	3	3	3		
	2. Unconscious but able to localise pain	2				
	3. Confusion	1			1	
	4. Not documented / Conscious	0				0
C. Blood smear for P. falciparum	1. Positive	2	2	2		
	2. Negative	1			1	
	3. None	0				0
D. Exclusion of other causes of altered mentation	1. Normal CSF	2	2	2		
	2. Normal random blood sugar	1	1			
	3. Not post-ictal coma	1	1			
	4. Normal urine	1	1			
	5. None	0			0	0
E. Treatment regimen prescribed	1. Quinine only	2	2			
	2. Quinine and antibiotic(s)	1		1	1	
	3. Other regimen	0				0
F. Clinical suspicion	1. Cerebral malaria	2	2	2		
	2. Severe malaria	1			1	
	3. Other diagnosis / None	0				0
Total			*16*	*11*	*5*	*0*

* Maximum score for definite cerebral malaria
† Minimum score for probable cerebral malaria
‡ Minimum score for probable cerebral malaria
§ Minimum score for 'not likely to be cerebral malaria'

Table F: The scores obtained from patient records retrieved from Kabale hospital who were recorded as having a final diagnosis of 'cerebral malaria' from 1st January 1999 to 31st December 2000.

Month/Year	Kabale Hospital admissions		
	No. recorded with diagnosis of CM*	No. whose records were available	No. with scores 5-16
1999			
January	1	0	0
February	0	0	0
March	2	1	1
April	0	0	0
May	0	0	0
June	1	1	1
July	0	0	0
August	0	0	0
September	2	2	2
October	1	0	0
November	1	0	0
December	2	0	0
2000			
January	0	0	0
February	2	2	0
March	0	0	0
April	2	0	0
May	3	3	0
June	1	1	0
July	1	0	0
August	2	1	0
September	10	9	1
October	5	1	0
November	1	0	0
December	5	4	1
Total	42	25	6
% of total	100	59.5	14.3
% where records available	NA	100	24

* Examined all files with a final diagnosis of severe malaria

Poster on guidelines for the 'Management of the Patient with Severe Malaria' for use at hospitals in Uganda that I played a role in developing for the Ministry of Health, Uganda and the Malaria Consortium, East Africa Office.

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