Aetiologies, neuroradiological features, and risk factors for mortality and long-term neurosequelae of febrile coma in Malawian children: a prospective cohort study

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Summary

Background Children in febrile coma in Africa are frequently hospitalised, with poorer outcomes than those in high-income settings. Cerebral malaria is historically the most common cause of febrile coma. Due to limited diagnostic and radiological resources and a decrease in malaria prevalence, there might be under-recognition of non-malarial coma. However, prospective data are scarce. We aimed to determine causes, neuroradiological features, risk factors for mortality, and neurosequelae of children in febrile coma in Malawi.

Methods In this prospective cohort study, we enrolled children in a coma (Blantyre Coma Scale score ≤2) who were aged between 3 months and 15 years at Queen Elizabeth Central Hospital, Blantyre, Malawi. We used pathogen-specific PCR analysis of blood and cerebrospinal fluid for 15 pathogens including *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Salmonella* spp, non-typhoidal *Salmonella*, *Salmonella enterica* serotype Typhi (*S* Typhi), *Klebsiella* spp, *Escherichia coli*, *Mycobacterium tuberculosis* (also using GeneXpert), *Streptococcus agalactiae*, herpes simplex virus (types 1 and 2), varicella zoster virus, cytomegalovirus, enteroviruses, and SARS-CoV-2; microscopy for malaria; admission brain MRI to enhance the diagnosis of cause and identify brain injury, swelling, and any other complications; and electroencephalography tracings were used identify subclinical seizures or non-convulsive status epilepticus. Assessment of malarial retinopathy was performed by a trained ophthalmologist. We used regression models to estimate risk factors for (and the difference in) 30-day mortality and 180-day neurosequelae (outcome assessed in-person) between children with non-malarial coma and cerebral malaria.

Findings Between Jan 31, 2018, and June 30, 2021, we recruited 352 children with febrile coma. Cerebral malaria was the most common cause (in 231 [66%] of 352 children). Pathogenic diagnosis was possible in 289 (82%) of 352 children. Co-infection was identified in 63 (27%) of 231 children with cerebral malaria, of which 49 (78%) were bacterial. The most common non-malarial causes of coma were meningitis (48 [14%] of 352 children) and encephalitis (24 [7%] of 352); 32 (9%) cases had an unknown cause. Compared with standard cultures, PCR significantly increased pathogen diagnosis (p<0·0001), with the highest yield in patients with meningitis (seven [15%] of 48 *vs* 30 [63%] of 48). *S pneumoniae* (n=44) and non-typhoidal salmonella or *S* Typhi (n=24) were the most frequently detected bacterial pathogens. Brain parenchymal abnormalities were identified on MRI in most children with febrile coma (165 [92%] of 178), and were significantly more common in children with non-malarial coma (68 [100%] of 68]) than cerebral malaria (98 [89%] of 110; p<0·0001). Overall, at 30 days after discharge, death (69 [21%] of 323) or any neurological impairment (163 [50%] of 323) were common, but poorer long-term outcomes were more frequent following non-malarial coma than cerebral malaria (death at 30 days: 32 [28%] of 114 *vs* 37 [18%] of 209, p=0·029; severe neurological impairment at 180 days: 19 [17%] of 114 *vs* 15 [7%] of 209, p=0·0079). Children who had cerebral malaria with CNS co-infection had higher mortality (ten [37%] of 27) than those with cerebral malaria alone (19 [12%] of 154, p=0·0033).

Interpretation Despite malaria control efforts, cerebral malaria remains the most common cause of febrile coma in Malawi. However, non-malarial coma causes a greater disease burden (death and disability), and a higher case-fatality rate was observed in non-malarial coma and cerebral malaria with non-malarial co-infection than cerebral malaria alone. To adequately treat severe invasive bacterial infections, that are frequently not detected in routine clinical practice, commencing empirical antimicrobials in all children in febrile coma, including those with cerebral malaria, could and should be rapidly implemented across Africa and must be considered. The study highlights the value of molecular diagnostics and imaging to guide diagnosis. The frequent findings of brain abnormalities from imaging at admission emphasises the need for earlier escalation of children with febrile coma to specialist care. Further work is needed to develop feasible molecular and radiological diagnostics for their successful deployment across the continent. Implementation of these methods could improve diagnosis and outcomes for children with febrile coma in Africa.

Lancet Glob Health 2025; 13: e1057–71

Published Online April 22, 2025 https://doi.org/10.1016/S2214-109X(25)00054-3

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For the Chichewa translation of the abstract see Online for appendix 1

For the French translation of the abstract see Online for appendix 2

For the Portuguese translation of the abstract see Online for appendix 3

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Funding Wellcome Trust.

Introduction

Children in febrile coma frequently present, are admitted to, and die in hospitals across sub-Saharan Africa.[1] In malaria-endemic regions, many of these cases are attributed to cerebral malaria (defined as Blantyre Coma Scale score ≤2, on a scale from 0 to 5, with lower scores indicating decreased levels of consciousness; peripheral parasitaemia with *Plasmodium falciparum* of any density; and no other discernible cause of coma).[2] Despite reduced malaria prevalence in the last few decades, limited molecular and radiological diagnostic resources and asymptomatic malaria parasitaemia in these settings contribute to the under-recognition of non-malarial coma.[3–5] The largest retrospectively investigated cohort of African (Kenyan) children in febrile coma to date identified a cause of the febrile coma in less than 50% of patients, with an increasing number of unknown causes of coma (due to limited non-malarial diagnostics) as the proportion of patients with cerebral malaria (versus non-malarial coma) decreased.[3] Leading severe malaria research centres have modelled estimates that approximately a third of children diagnosed with severe malaria have undiagnosed non-malarial (probably bacterial) causes for their presentation.[6–8] Differentiating

Research in context

Evidence before this study

Febrile coma is a frequent hospital presentation among African children. Due to limited diagnostic and radiological resources, treatment for febrile coma is often empirical. Parenteral antibiotics are often withheld if a hospitalised African child has a positive blood smear for *Plasmodium falciparum*, leading to a potential undertreatment of bacterial co-infection. Historically, studies have provided sparse information on the causes, clinical and neuroimaging features, and long-term outcome data among these children. In parallel with this study, we conducted a systematic review and meta-analysis of the causes and outcomes of non-traumatic coma in African children, searching publications from the database inception to Feb 9, 2024, across MEDLINE, Embase, and Scopus databases. We identified 138 relevant studies but only 23 provided data on multiple causes of coma—of these, only six were prospective coma studies, including three small cohorts in sub-Saharan Africa since 2000. Most studies had limited diagnostic reporting, with most molecular diagnostics targeting viruses. Only one study briefly described neuroimaging findings. No African study has prospectively specifically examined the causes of child febrile coma by applying bacterial and viral PCR to blood and cerebrospinal fluid combined with MRI neuroimaging. Similarly, long-term follow-up disability estimates across different coma causes have not been reported.

Added value of this study

To our knowledge, this Malawian prospective study provides the largest cohort of febrile coma in children in Africa. Investigations of coma cause included microbiological and molecular examination of blood and spinal fluid of children for 15 pathogens (bacteria and viruses), as well as MRI at admission. We also conducted face-to-face neurological follow-up assessments of survivors. Overall, the study offers a current and comprehensive description of both causes and risk factors for mortality and long-term neurosequelae. Cerebral malaria remains the most common cause of febrile coma. Consistent with prior modelling estimates, for the first time, we confirm (mostly bacterial) co-infection was detected in more than a quarter of cerebral malaria cases. Non-malarial pathology was associated with a significantly higher mortality in both children with non-malarial coma and cerebral malaria with co-infection compared with cerebral malaria alone. MRI imaging showed a high frequency and range of brain abnormalities, including surgically amenable complications, across multiple causes of febrile coma. Use of molecular diagnostics significantly increased pathogen yield compared with routine culture. Neurological follow-up showed that disability was present in more than half of the survivors.

Implications of all the available evidence

The high proportion and poorer outcomes of bacterial infections among children with febrile coma, including children with cerebral malaria co-infection, emphasises the need to urgently reconsider front-line management of these children. The study also found significantly lower mortality in children with coma caused by cerebral malaria and a co-infection who received antimicrobials compared with those who did not receive antimicrobials. Together these findings emphasise the need for immediate antibiotic provision for children presenting with fever and coma, irrespective of malaria diagnosis. These data have been made available to support updates of national and WHO guidelines on severe malaria and coma. Our evidence has the potential to catalyse change in practice and save lives. Our findings also highlight the value of enhanced diagnostics, both molecular and neuroimaging, to improve diagnosis and guide management. The frequent brain abnormalities and complications on admission MRI suggest earlier escalation to specialist care—ideally care with neurosurgical capacity—could improve outcomes. Further work is needed to develop feasible molecular and radiological diagnostics for widescale deployment and adoption across the continent. Beyond improved diagnostics, research (both basic and operational) to understand and overcome the ongoing poor outcomes in febrile coma is needed.

severe malarial and bacterial infections clinically is difficult, and co-infection is suspected to be common. WHO therefore recommends that children with suspected severe malaria, including cerebral malaria, receive both parenteral antimalarials and antibiotics.[6,9] However, antibiotics are often delayed or never given.[2] The burden of CNS infections is greatest in sub-Saharan Africa,[10] and implementing rapid diagnostics to optimise treatment in the presence of proliferating antimicrobial resistance (alongside reducing both death and disability after brain infections), are all priorities of the WHO Defeating Meningitis global road map.[10,11] To address the scarcity of prospective data and inform future clinical management, we aimed to determine the causes, neuroradiological features, risk factors for mortality, and long-term neurosequelae of febrile coma. We hypothesised that mortality estimates differ significantly between cerebral malaria and non-malarial coma (with higher mortality in non-malarial coma) and that febrile coma can be caused by a wide spectrum of pathogens that are often unidentified in routine clinical practice.

Methods

Study design and participants

This prospective cohort study recruited children from Queen Elizabeth Central Hospital in Blantyre, Malawi, which is a setting with endemic *P falciparum* malaria that admits 30 000 children per year. Malawi is a low-income country[12] with low health-care expenditure (3% of gross domestic product).[13] An estimated 84 000 children live with HIV[14] and 40% have stunted growth.[15]

We enrolled children aged 3 months to 15 years who were febrile (≥38·0°C on admission, or history of fever within 72 h) and in a deep coma (defined as Blantyre Coma Score [BCS] ≤2, on a scale from 0 to 5, with a lower score indicating decreased levels of consciousness [appendix 4 p 1]) for more than 4 h, who had suspected CNS infection, and whose parent or guardian had provided written informed consent for study participation. We excluded children with a BCS score of 2 or less or who had been in deep coma for less than 4 h; children who had a history of traumatic brain injury, neurosurgery, neurodisability, or refractory epilepsy; or where the caregiver was unable to provide consent or did not speak English or Chichewa (appendix 4 p 2).

The study protocol was granted ethical approval by the University of Malawi College of Medicine Research Ethics Committee (P09/17/2265) and the University of Liverpool Research Ethics Committee (UoL001338). The University of Liverpool acted as the study sponsor.

Procedures

Enrolled children were cared for in a high-dependency paediatric research ward. We used the Epilepsy Screening Questionnaire[16] to exclude children with unreported complex epilepsy (epilepsy complicated by neurodisability) and the Ten Questions[17] measure to screen for neurodisability (both validated onsite with good sensitivity) to prevent confounding neurocognitive outcomes.[18] Pre-hospital data (eg, coma duration, pre-hospital antibiotic and antimalarial use) were recorded as reported by guardians or as reported in the child's community health passport. In cases of discrepancy, the health passport was relied upon as a government health document. Extensive case report forms were populated at recruitment, and detailed examination was performed twice daily until the child's death or discharge.

We performed blood sampling for culture, biochemistry, and haematology (appendix 4 p 5).[19] Lumbar puncture, with a flexible manometer for opening pressure, was performed to collect cerebrospinal fluid for diagnostic purposes unless contraindicated (per clinical judgement).[2] Cerebrospinal fluid was analysed using microscopy, Gram staining, and culture. Stored blood and cerebrospinal fluid underwent extensive study-specific diagnostics, including molecular testing for pathogen detection. We undertook PCR testing for the following pathogens: *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, non-typhoidal *Salmonella*, *Salmonella typhi*, *Klebsiella* spp, *Escherichia coli*, *Mycobacterium tuberculosis* (also measured using GeneXpert), *Streptococcus agalactiae*, herpes simplex virus 1 and 2, varicella zoster virus, cytomegalovirus, and enteroviruses. SARS-CoV-2 PCR testing was performed on cerebrospinal fluid from the date of the first reported COVID-19 case in Malawi (appendix 4 pp 5–12). Malaria microscopy, for both thick and thin blood films, was performed to determine peripheral blood parasitaemia with *Plasmodium falciparum* of any density.

Children were defined as living with HIV if they were HIV antibody test positive and prescribed antiretroviral therapy before this admission episode, or HIV antibody test positive upon admission and immunosuppressed from their HIV infection if at infection stage 2 or 3 (based on the Centers for Disease Control and Prevention age-specific CD4 count [appendix 4 p 44] and detectable viral load [≥50 copies per mL where taken] or self-report not adhering to antiretroviral therapy at admission).

Brain MRI was performed within 6 h of admission using a 0·35-T Signa Ovation Excite MRI scanner (General Electric, Boston, MA, USA). All non-malarial images and a third of cerebral malaria images (due to logistical constraint) were blindly interpreted and reported by two neuroradiologists using the data collection tool REDCap (version 8.6.2, appendix 4 pp 14–31). The following non-contrast sequences were performed: axial T2, sagittal T1, coronal T2 fluid-attenuated inversion recovery, diffusion-weighted imaging, and axial gradient echo. Overall brain volume was scored based on the appearance of the cerebral hemispheres on a scale from 1 to 8. The remaining cerebral malaria images were reported by one neuroradiologist (RD onto REDCap; appendix 4

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See **Online** for appendix 4

pp 14–31). Admission electroencephalograms (EEGs) were recorded using a Ceegraph digital machine (BioLogic, Pleasanton, CA, USA).[20] EEGs were systematically reviewed and reported (REDCap) by one of two neurologists (DP, GB) trained in EEG interpretation (appendix 4 p 31).

Children with clinical cerebral malaria (appendix 4 pp 2–4) were treated with intravenous artesunate at admission (<20 kg 3·0 mg/kg; ≥20 kg 2·4 mg/kg), then at 12 h and 24 h, then stepped down to oral lumefantrine artemether antimalarials (number of tablets and dosage dependent on weight) per Malawi Ministry of Health guidelines.[21] The use of adjunctive therapies, including intravenous ceftriaxone, were decided by the admitting clinician. Children whose coma was non-malarial (BCS ≤2 without peripheral parasitaemia, determined by malaria microscopy [appendix 4 p 4]), were treated with intravenous ceftriaxone, and occasionally escalated to intravenous carbapenems, intravenous adjunctive aminoglycosides, or both, if clinically indicated and in stock. Assessment of malarial retinopathy[2] (appendix 4 pp 2–4) was performed by a trained ophthalmologist.

Children who survived hospital admission returned at 30 days and 180 days after discharge for detailed neurodisabililty assessment, which was performed in person by dedicated neurodisability research nurses using the Liverpool Outcome Score that was validated for use in Malawi.[22,23] Hearing was assessed at 180 days by a trained audiologist (appendix 4 pp 5–12). Regular in-person field tracing took place to encourage scheduled follow-up.

Statistical analysis

Statistical approaches are described in detail in the appendix 4 (pp 5–12). The study was powered (80% power, 5% significance level) to detect a minimum risk ratio of 2·5 in the proportion of 30-day mortality between participants with non-malarial coma compared with cerebral malaria (assuming a 15% mortality rate associated with cerebral malaria). Our target sample size was 350 (220 cerebral malaria, 130 non-cerebral malaria) to detect this difference in mortality, and to give a comprehensive description of the causes of febrile coma. Normality of data was assessed using D'Agostino–Pearson Omnibus normality tests. Group comparisons were tested with Student's *t* tests (or Mann–Whitney *U* tests for non-normal data) for continuous variables and χ^2 (or Fisher's exact test where expected counts were less than ten) for categorical variables, with two-sided p values of less than 0·05 considered statistically significant. The Kruskal–Wallis test with Dunn's multiple group comparison testing procedure was used to determine any significant difference in non-parametric continuous variables. ANOVA was used for parametric multiple group testing. Kaplan–Meier estimates of the survival function were generated, stratified by different causes, and the log-rank test was used to test any significant differences. We constructed logistic regression multivariable models for candidate risk factors for 30-day mortality and 180-day disability. Statistical analysis was performed with Stata (version 15.1) and GraphPad Prism (version 9.0.0).

Role of the funding source

This study was funded by the Wellcome Trust (Clinical PhD Fellowship, University of Liverpool block award grant number 203919/Z/16/Z and Wellcome core award 206545/Z/17/Z). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Jan 31, 2018, to June 30, 2021, we recruited 352 children to the study. 189 (54%) children were male, 163 (46%) were female, and all children admitted were Malawian (table 1). Patient demographics, clinical features, investigations, management, and discharge outcomes are shown in table 1 and the appendix 4 (pp 39–42). The median age of participants was 53 months (IQR 33–78) for children with cerebral malaria coma versus 54 months (30–100) for non-malarial coma. More children younger than 5 years with non-malarial coma were severely malnourished (five [8%] of 61) compared with children with cerebral malaria (one [1%] of 132; p=0·013).

Parasitology, PCR, and MRI facilitated a syndromic diagnosis (ie, fitting the case definition irrespective of whether a pathogen was detected or not) in 320 (91%) of 352 children, and pathogenic diagnosis in 289 (82%) children (figure 1, appendix 4 pp 31–34). 231 (66%) children had cerebral malaria and 121 (34%) children had non-malarial coma. Co-infection was seen in 63 (27%) of 231 children with cerebral malaria (27 [12%] with meningitis and 36 [16%] with a bloodstream infection). Bacterial co-infection was present in 49 (78%) children, and viral co-infection was present in 14 (22%) children (appendix 4 pp 34). We identified a new phenotype of post-cerebral malaria coma (appendix 4 p 4).[14] We found that non-malarial causes of febrile coma were acute meningitis (48 [14%] of 352), encephalitis (24 [7%]), septic encephalopathy (13 [4%]), and unknown causes (32 [9%]; figure 1, appendix 4 pp 33–34).

Few clinical features at admission differed between patients with cerebral malaria and non-malarial coma. Coma duration before admission was longer in children with non-malarial coma (24 h [IQR 10–48]) versus those with cerebral malaria (16 h [7–24]; p=0·0002). Before hospital admission, compared with cerebral malaria, the proportion of children with non-malaria coma who received antibiotics was higher (109 [91%] of 120 *vs* 141 [61%] of 231, p<0·0001) and who received antimalarials was fewer (89 [74%] of 121 *vs* 228 [99%] of 231, p<0·0001). Almost all children were febrile (98%) prior to admission and fever persisted for 2–720 h. Many children remained

	All cases (n=352)			Cerebral malaria (n=231)				Non-malarial coma (n=121)					
	Cerebral malaria (n=231)	Non-malarial coma (n=121)	p value*	Cerebral malaria only (n=154)	Cerebral malaria and meningitis (n=27)	Cerebral malaria and BSI (n=36)	Post-cerebral malaria (n=14)	Acute meningitis (n=48)	Encephalitis (n=24)	Septic encephal-opathy (n=13)	Unknown encephal-opathy (n=32)	Other (n=4)†	p value*
Age, months	53 (33–78)	54 (30–100)	0·34	55 (33–75)	47 (33–75)	57 (32–78)	59 (41–99)	67 (33–126)	44 (17–104)	76 (36–85)	48 (30–84)	82 (56–125)	0·21
Sex			0·65										0·42
Male	122 (53%)	67 (55%)		82 (53%)	15 (56%)	15 (42%)	7 (50%)	25 (52%)	12 (50%)	6 (46%)	20 (63%)	4 (100%)	
Female	109 (47%)	54 (45%)		72 (47%)	12 (44%)	21 (58%)	7 (50%)	23 (48%)	12 (50%)	7 (54%)	12 (37%)	0/4	
Severe malnutrition (MUAC Z score <3) in children aged <5 years (%)	1/132 (1%)	5/61 (8%)	0·0080	1/88 (1%)	0/16	0/20	0/8	3/20 (15%)	2/15 (13%)	0	0	0	0·047
Underlying comorbidity													
HIV positive	13/231 (6%)	15/121 (12%)	0·025	8/154 (5%)	3/27 (11%)	1/36 (3%)	1/14 (7%)	9/47 (19%)	4/24 (17%)	0/13	2/32 (6%)	0/4	0·029
Immunosuppressed	6/231 (3%)	14/121 (12%)	0·0010	2/154 (1%)	2/27 (7%)	1/36 (3%)	1/14 (7%)	9/48 (19%)	4/24 (17%)	0/13	1/32 (3%)	0/4	<0·0001
Before admission													
Fully vaccinated	174/199 (87%)	102/114 (89%)	0·14	123/154 (80%)	21/24 (88%)	28/29 (97%)	10/10 (100%)	41/44 (93%)	19/23 (83%)	11/13 (85%)	28/31 (90%)	3/3 (100%)	0·12
Duration of coma before admission, h	16 (7–24), n=229	24 (10–48), n=120	0·0002	16 (8–24)	16·0 (7–37)	12·0 (5–21)	24·0 (18–48)	24·5 (10·5–72)	24·5 (11–33)	16·5 (6–48), n=12	24·0 (9–48)	17·5 (10·5–60)	0·0029
History of seizure	151/230 (66%)	91/121 (75%)	0·066	98/153 (64%)	15/27 (56%)	26/36 (72%)	12/14 (86%)	31/48 (65%)	19/24 (79%)	11/13 (85%)	27/32 (84%)	3/4 (75%)	0·16
Antimalarials before admission	228/231 (99%)	89/121 (74%)	<0·0001	151/154 (98%)	27/27 (100%)	36/36 (100%)	14/14 (100%)	35/48 (73%)	12/24 (50%)	11/13 (85%)	28/32 (88%)	3/4 (75%)	<0·0001
Antibiotics before admission	141/231 (61%)	109/120 (91%)	<0·0001	94/154 (61%)	21/27 (78%)	16/36 (44%)	11/14 (79%)	46/48 (96%)	22/24 (92%)	9/13 (69%)	27/32 (84%)	4/4 (100%)	<0·0001
Clinical signs													
Blantyre Coma Scale	2 (1–2)	1 (1–2)	0·0031	2 (1–2)	2 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)	1 (1–2)	1 (1–2)	1·5 (1–2)	0·096
Heart rate, beats per min	142 (127–159)	135 (117–160)	0·087	143 (130–159)	140 (120–160)	145 (128–163)	124 (111–138)	125 (113–148)	132 (112–152)	152 (125–162)	146 (132–164)	118 (104–133)	0·023
Clinical features													
Seizures during admission	65/231 (28%)	51/121 (42%)	0·024	41/154 (27%)	8/26 (30%)	12/36 (33%)	4/14 (29%)	22/48 (46%)	9/24 (38%)	6/13 (46%)	14/32 (44%)	0/4	0·19
Neck stiffness	3/231 (1%)	15/121 (12%)	<0·0001	3/154 (2%)	0/27	0/36	0/14	13/48 (27%)	2/24 (8%)	0/13	0/32	0/4	<0·0001
Decorticate posturing	24/231 (10%)	5/121 (4%)	0·043	19/154 (12%)	3/27 (11%)	2/36 (6%)	1/14 (7%)	0/48	0/24	1/13 (8%)	3/32 (9%)	0/4	0·11
Malarial retinopathy positive	146/230 (63%)	5/109 (5%)	0·0026	93/153 (61%)	22/27 (81%)	24/36 (67%)	9/13 (69%)	1/42 (2%)	0/21	0/11	4/31 (13%)	0/4	<0·0001
Investigations													
Median C-reactive protein, mg/L	160 (87–200), n=224	118 (56–199), n=116	0·0015	157 (70–200), n=151	158 (99–200), n=26	188 (102–200), n=34	152 (116–200), n=13	135 (58–200), n=47	140 (79–200), n=23	84 (52–130)	96 (44–200), n=29	51 (30–69)	0·42
Plasma white cell count, $\times 10^9$/L	9·1 (6·5–12·7)	12·5 (7·7–17·5), n=120	0·0002	9·1 (6·8–11·8)	13·2 (6·7–17·8)	9·1 (6–11·9)	8·3 (4·9–18·4)	12·7 (7·8–19)	13·6 (8·2–22·4)	12·6 (8·8–17·7)	11·1 (6·8–13·6), n=31	13·5 (2·5–22·3)	0·0094

(Table 1 continues on next page)

	All cases (n=352)			Cerebral malaria (n=231)				Non-malarial coma (n=121)					
	Cerebral malaria (n=231)	Non-malarial coma (n=121)	p value*	Cerebral malaria only (n=154)	Cerebral malaria and meningitis (n=27)	Cerebral malaria and BSI (n=36)	Post-cerebral malaria (n=14)	Acute meningitis (n=48)	Encephalitis (n=24)	Septic encephal-opathy (n=13)	Unknown encephal-opathy (n=32)	Other (n=4)†	p value*
(Continued from previous page)													
Platelet count, ×10⁹/L	74 (38–129)	276 (155–390), n=120	<0·0001	67 (38–125)	68 (29–104)	93 (41–137)	129 (69–220)	311·5 (131·5–538·5)	276·5 (198·5–355)	299 (45–361)	258 (155–358), n=31	147·5 (52–217)	0·0001
Haematocrit, %	24 (20·5–28·3)	30 (24·1–33·5), n=120	<0·0001	24·5 (20·6–28·3)	22·8 (19·8–26)	23·7 (19·3–29·4)	26·2 (22·4–34·5)	30·7 (25·3–33·1)	29·75 (24·8–36·5)	27·7 (23·3–33·5)	29·6 (23·4–32·1)	30·5 (10·9–31·8)	0·0001
Urea, mmol/L	7·6 (4·9–11), n=204	6·5 (3·7–9·5), n=83	0·058	7·3 (4·5–10·5), n=139	8·1 (6–13·2), n=25	8·2 (94·6–14·8), n=32	7 (4·6–50·4), n=9	6·5 (4·5–10·5), n=39	7·2 (5·4–9·6), n=18	8·4 (4·7–11·4), n=7	6 (2·8–7), n=18	37·2, n=1	0·12
Parasitaemia, parasites/mm³	854 (230–61 200)	..	..	1020 (240–76 250)	792 (145–30 500)	536 (225–73 440)	..	..	..	..	..	..	..
Lactate, mmol/L	3·6 (2·3–6·4)	3·6 (1·9–6·4)	0·29	3·6 (2·2–6·8)	3·7 (3–5·5)	4·1 (2·7–8·3)	2·2 (1·3–3·2)	3·6 (2–5·1)	5·1 (2·1–7·6)	5·1 (3·1–7·5)	2·7 (1·6–5·6)	4·5 (1·4–8·3)	0·016
CSF opening pressure, mm	158 (115–220), n=227	165 (90–230), n=115	0·61	160 (120–210)	180 (140–260)	130 (95–180)	140 (100–265)	160 (90–233), n=44	150 (90–190), n=23	175 (100–220), n=12	158 (85–215)	270 (210–335)	0·18
CSF white cell count >4 cells/mm³	32/231 (14%)	47/121 (39%)	<0·0001	11/154 (7%)	18/27 (67%)	0/36	3/14 (21%)	39/48 (81%)	6/24 (25%)	0/13	1/32 (3%)	0/4	<0·0001
CSF protein g/L	0·3 (0·19–0·48), n=230	0·37 (0·23–1·1), n=116	0·002	0·31 (0·18–0·47), n=153	0·4 (0·2–0·64)	0·27 (0·21–0·42)	0·29 (0·17–1·43)	0·93 (0·35–2·09), n=45	0·4 (0·19–1·00)	0·34 (0·29–0·52), n=12	0·25 (0·2–0·36), n=31	0·34 (0·23–0·67)	0·0001
Elevated CSF protein, >0·40 g/L	79/230 (34%)	60/113 (53%)	0·0010	50/154 (33%)	14/25 (56%)	9/36 (25%)	6/14 (43%)	34/41 (83%)	13/23 (56%)	6/13 (46%)	6/32 (19%)	1/4 (25%)	<0·0001
Abnormal CSF:blood glucose ratio	26/226 (12%)	30/117 (26%)	0·0030	19/151 (13%)	4/26 (15%)	3/35 (9%)	0/14	20/46 (43%)	4/24 (17%)	2/12 (17%)	4/31 (13%)	0/4	0·0040
Abnormal CSF profile‡	106/231 (46%)	79/119 (66%)	0·0010	64/154 (42%)	23/27 (85%)	12/36 (33%)	7/14 (50%)	45/47 (96%)	17/24 (71%)	6/12 (50%)	10/32 (31%)	1/4 (25%)	<0·0001
Epileptiform activity on admission EEG	12/205 (6%)	9/78 (12%)	0·13	8/140 (6%)	4/23 (17%)	0/29	0/13	1/28 (4%)	1/18 (6%)	1/4 (25%)	5/23 (23%)	0/4	0·020
Abnormal MRI§	68/68 (100%)	98/110 (89%)	<0·0001	65/67 (97%)	14/14 (100%)	18/27 (67%)	1/1 (100%)	33/33 (100%)	19/19 (100%)	7/7 (100%)	9/9 (100%)	0/4	<0·0001
Management and treatment													
Intravenous antibiotics in teaching hospital	94/231 (41%)	114/121 (94%)	<0·0001	60/154 (39%)	10/27 (37%)	14/36 (39%)	10/14 (71%)	47/48 (98%)	23/24 (96%)	12/13 (92%)	30/32 (94%)	3/4 (75%)	<0·0001
Intravenous antimalarials in teaching hospital	228/231 (99%)	52/121 (43%)	<0·0001	153/154 (99%)	27/27 (100%)	36/36 (100%)	12/14 (86%)	15/48 (31%)	7/24 (29%)	6/13 (46%)	24/32 (75%)	4/4 (100%)	<0·0001
Antiepileptics in teaching hospital	90/231 (39%)	65/121 (54%)	0·0080	58/154 (38%)	13/27 (48%)	14/36 (39%)	6/14 (43%)	25/48 (52%)	10/24 (42%)	10/13 (77%)	19/32 (59%)	0/4	0·0090

(Table 1 continues on next page)

	All cases (n=352)			Cerebral malaria (n=231)				Non-malarial coma (n=121)					
	Cerebral malaria (n=231)	Non-malarial coma (n=121)	p value*	Cerebral malaria only (n=154)	Cerebral malaria and meningitis (n=27)	Cerebral malaria and BSI (n=36)	Post-cerebral malaria (n=14)	Acute meningitis (n=48)	Encephalitis (n=24)	Septic encephalopathy (n=13)	Unknown encephalopathy (n=32)	Other (n=4)†	p value*
(Continued from previous page)													
Outcome													
Disability at discharge	34/231 (15%)	39/121 (32%)	<0·0001	22/154 (14%)	3/27 (11%)	5/36 (14%)	5/14 (36%)	19/48 (40%)	8/24 (33%)	1/13 (8%)	9/32 (28%)	0/4	<0·0001
Death at discharge	33/231 (14%)	27/121 (21%)	0·062	19/154 (12%)	10/27 (37%)	4/36 (11%)	0/14	13/48 (27%)	3/24 (13%)	5/13 (38%)	4/32 (13%)	2/4 (50%)	0·0014

Data are median (IQR), n (%), or median (IQR), n. p values were estimated with the use of Student's *t* tests for means, Wilcoxon rank-sum tests for medians, and Pearson's χ^2 tests for proportions, except when noted otherwise. CSF=cerebrospinal fluid. EEG= electroencephalogram. MUAC=mid-upper arm circumference. *Multivariate testing on mean. Multiple group testing of proportions was performed by χ^2, ANOVA for (parametric) means, and Kruskal–Wallis for (non-parametric) medians. †Malignancy (n=2), haemolytic uraemic syndrome (n=1), hepatic encephalopathy (n=1). ‡Defined as either raised CSF white cell count (>4 × 10^6 cells/L), raised protein (>0·5 g/L), or CSF:blood glucose ratio (<0·5). §Any central nervous system abnormality identified by the trained neuroradiologist. For further information on immunosuppression, see appendix 4 (p 43). BSI=bloodstream infection.

Table 1: **Demographics, clinical features, investigations, management, and discharge outcome of study population grouped by cerebral malaria, non-malarial coma, and both cerebral malaria and non-malarial coma subgroups**

febrile at recruitment (246 [70%] of 352), despite most receiving antipyretics at admission (289 [82%]). 290 (82%) experienced fever during hospitalisation, with median fever clearance taking 10 h (IQR 2–37 h; appendix 4 pp 57–58]. Children in a non-malarial coma presented in a deeper coma (median Blantyre Coma Scale score 1 [non-malarial coma] *vs* 2 [cerebral malaria]; p=0·0031) and a higher proportion had seizures (51 [42%] of 121 *vs* 65 [28%] of 231; p=0·024), when compared with children with cerebral malaria. Neck rigidity was observed in a higher proportion of children with non-malarial coma (15 [12%] of 121; mostly due to meningitis [27%]) than those with cerebral malaria (three [1%] of 231; p<0·0001). Features of malarial retinopathy were more frequently identified in cerebral malaria (63%) than non-malarial coma (5%; mostly due to unknown cause of encephalopathy [13%]; p<0·0001).

A higher proportion of children with non-malarial coma (15 [12%] of 121) were living with HIV than those with cerebral malaria (13 [6%] of 231; p=0·026), and those living with HIV were frequently immunosuppressed (14 (93%) of 15 children with non-malarial coma *vs* 6 (46%) of 13 with cerebral malaria; p=0·01). CD4 counts were low (median cells per µl 239 [IQR 97–595] in non-malarial coma *vs* 400 [231–765] in cerebral malaria) and viral loads were high (copies per mL 183 000 [IQR 2187–1·7 million] for non-malarial coma *vs* 203 000 [353–224 000] for cerebral malaria; table 1; appendix 4 p 44).

Every child had an admission aerobic blood culture taken, and 350 (99%) underwent a lumbar puncture (two children did not due to severe focal neurology (appendix 4 pp 36–37). PCR significantly increased non-malarial pathogenic diagnosis versus culture alone in children with cerebral malaria (one [<1%] of 231 *vs* 49 [21%] of 231; p<0·0001) and those with non-malarial coma (eight [7%] of 121 *vs* 48 [40%] of 121; p<0·0001), with the highest molecular yield in meningitis (seven [15%] of 48 *vs* 30 [63%] of 48; p=0·0001). PCR detected at least one pathogen in the cerebrospinal fluid, blood, or both, in 97 (28%) children across all causes of febrile coma. 56 of these PCR-detected pathogens supported a diagnosis of brain infection and 39 a bloodstream infection; most PCR-detected pathogens were bacterial (77 [22%]), with viral (18 [5%]) the next most common across the entire febrile coma cohort. For the entire cohort, *S pneumoniae* (n=44), followed by *Salmonella* spp (n=24; non-typhoidal salmonella [n=18] and *S* Typhi [n=6] combined) were the most frequently detected bacteria in both blood and cerebrospinal fluid in cerebral malaria and non-malarial coma (figure 1). PCR also detected *Klebsiella* spp, *Escherichia coli*, and *Mycobacterium tuberculosis*. Enterovirus (n=5) and cytomegalovirus (n=5) were the most common viruses, followed by HSV-1, HSV-2, varicella zoster virus, and SARS-CoV-2.

After the lumbar puncture, 178 (51%) children underwent admission brain MRI. No children suffered brain herniation or cardiac arrest immediately after lumbar

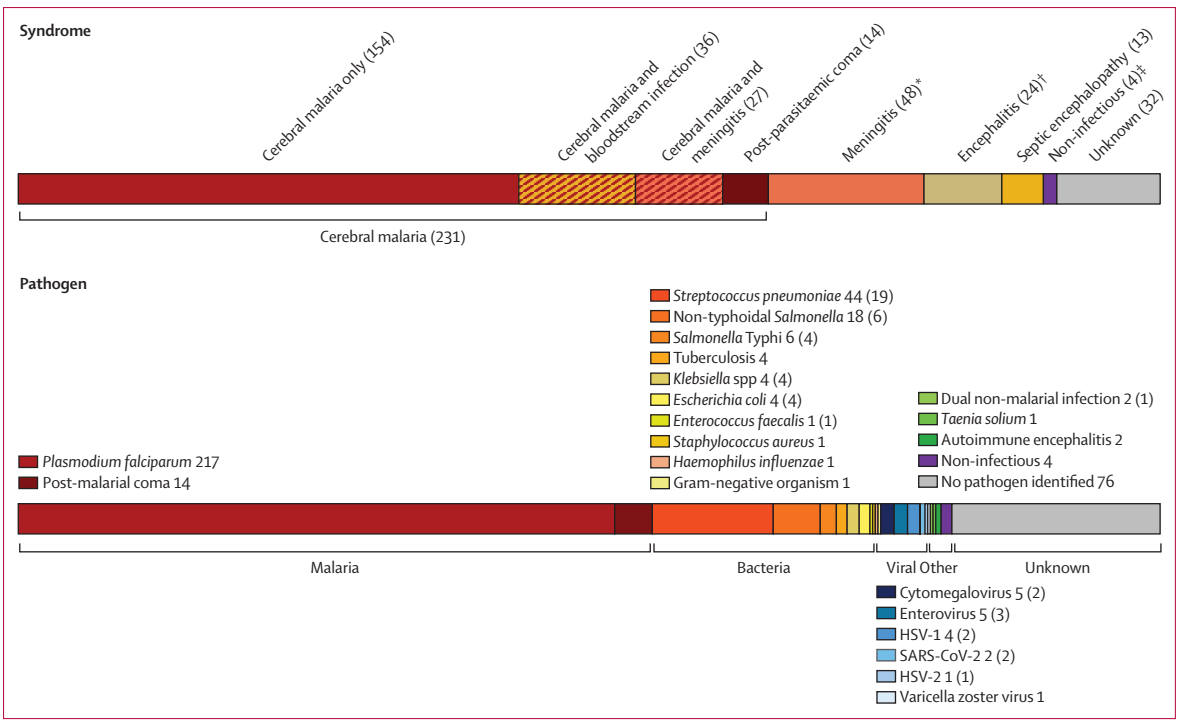

Figure 1: **Stacked bar chart illustrating the syndromic and pathogenic diagnosis of coma in included participants**
*Subdiagnoses of meningitis as follows: acute bacterial meningitis (n=29); acute viral meningitis (n=1); unknown meningitis (n=13); tuberculous meningitis (n=3); meningitis originating outside CNS (n=2 [1 endocarditis, 1 neurocysticercosis]). †Subdiagnoses of encephalitis as follows: infectious encephalitis (n=10); acute disseminated encephalomyelitis (all with pathogens [n=4]); autoimmune encephalitis (n=2); unknown encephalitis (n=8). ‡Subdiagnoses of non-infectious causes as follows: malignancy (n=2); hepatic encephalopathy (n=1); haemolytic uraemic syndrome (n=1). Bracketed numbers next to pathogen indicate the number of times the pathogen was found as a co-infection with *Plasmodium falciparum*.

puncture. 166 (92%) scans were abnormal (68 [100%] of 68 in children with non-malarial coma *vs* 98 [89%] of 110 in those with cerebral malaria, p=0·0038; table 1), including cerebral oedema in almost half of all children who underwent MRI (83 [50%]). A higher total median number of parenchymal abnormalities were seen in non-malarial coma (14 [12–16]) than cerebral malaria (9 [0–14]; p<0·0001; table 1, figures 2 and 3). Specific complications were more frequently seen in meningitis (both meningitis alone and cerebral malaria with meningitis co-infection) than cerebral malaria, with infarction identified in a quarter of meningitis cases (8 [24%] of 33 *vs* 0 [0%] of 67, p<0·0001), as well as complications potentially amenable to surgery such as sinus collections (27 [82%] of 33 *vs* 25 [37%] of 67, p<0·0001), subdural collections (6 [18%] of 33 *vs* 0 [0%] of 67, p=0·0009), and hydrocephalus (8 [24%] of 33 *vs* 1 [1%] of 67, p=0·0005; figure 2; appendix 4 p 38).

Median serum C-reactive protein (CRP) levels were above the threshold (80 mg/L) considered indicative of invasive bacterial infection[25] in patients with cerebral malaria, non-malarial coma, and cerebral malaria and non-malarial co-infection (appendix 4 p 43). Median peripheral white cell count was higher in children with non-malarial coma (12·5×10⁹/L [IQR 7·7–17·5]) than those with cerebral malaria (9·1×10⁹/L [6·5–12·7]; p=0·0002). In children with cerebral malaria, peripheral white cell count was higher in children with bacterial CNS co-infection (13·2×10⁹/L [6·7–17·8]) than those with cerebral malaria alone (9·1×10⁹/L [6·8–11·8]; p=0·0002; appendix 4 pp 46–48). Platelet count was lower in children with cerebral malaria (74×10⁹/L [38–129]) than those with non-malarial coma (276×10⁹/L [155–390]; p<0·0001). Increased blood lactate, indicative of metabolic acidosis, was elevated for all causes (>2 mmol/L).

A higher proportion of children with non-malarial coma (versus those with cerebral malaria) had cerebrospinal fluid pleocytosis (47 [39%] of 121 *vs* 32 [14%] of 231; p<0·0001), raised cerebrospinal fluid protein (60 [53%] of 113 *vs* 79 [34%] of 230; p=0·0010), and an abnormal cerebrospinal fluid:blood glucose ratio (30 [26%] of 117 *vs* 26 [12%] of 226, p=0·0030). Meningitis (46 [96%] of 48) and encephalitis (17 [71%] of 24) had the most frequently abnormal cerebrospinal fluid picture (pleocytosis, raised protein, or abnormal cerebrospinal fluid:blood glucose ratio) among the children with non-malarial coma, and cerebral malaria and meningitis co-infection had the most frequently abnormal cerebrospinal fluid picture among the children with cerebral malaria (23 [85%] of 27; table 1, appendix 4 p 45). More children with cerebral malaria and CNS co-infection also had raised cerebrospinal fluid white cell count than

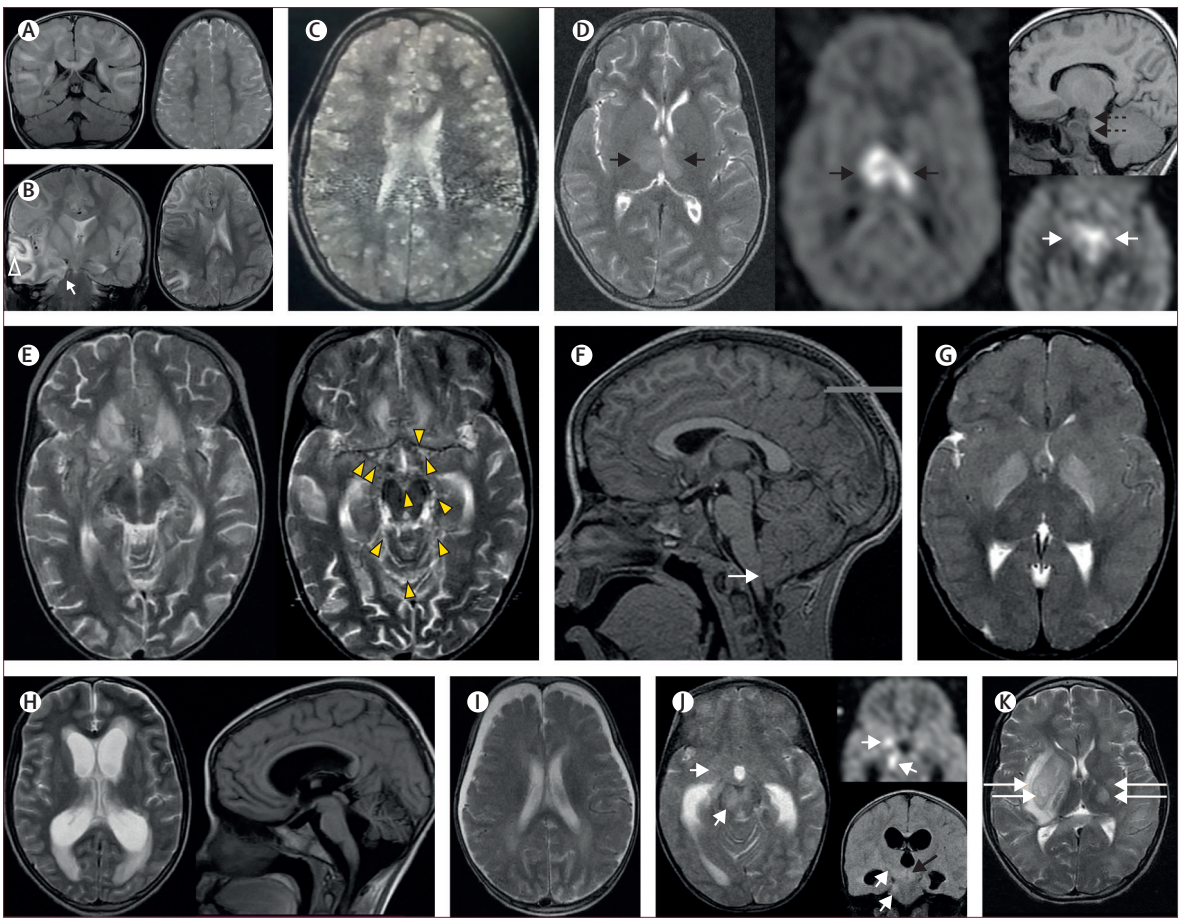

Figure 2: **Admission MRI brain scans illustrating examples of neuroimaging that: supported clinical causal diagnosis (A–K), showed the complications of meningitis (D,E, H–K; including surgically amenable complications [D, H–K]), enabled specific diagnoses not achievable without neuroimaging (C, D), and illustrated characteristic radiological features of specific causes (A–C, F, G)**

(A) Boy aged 3 years with enterovirus CNS infection with a presentation congruous with ADEM. Bilateral symmetrical T2 axial (left) and FLAIR coronal (right) hyperintensities affecting the subcortical white matter, descending white matter tracts, and corpus callosum. (B) Boy aged 5 years with herpes simplex virus type 1 encephalitis: axial (left) and coronal (right) T2-weighted images show bilateral frontal, parietal, temporal, cortical, and subcortical restriction. There is cortical necrosis (open arrow) and substantial mass effect with uncal herniation (white arrow). (C) Boy aged 13 years with neurocysticercosis: chronic severe headache then coma with pathognomonic diffuse intracranial cysts on axial T2-weighted imaging. Father was a pig farmer and subsequently identified to have diffuse peripheral tissue (thigh) cysticerci. (D) Girl aged 12 years with *Staphylococcus aureus* meningitis: axial T2-weighted and diffusion imaging illustrates an infarct in the artery of percheron with bilateral medial thalamic involvement with associated diffusion restriction (arrows). This infarct is likely a sequelae of arteritis due to infective material within the suprasellar cistern from a pituitary abscess (dotted arrows on the sagittal T1 image) that also shows restricted diffusion (white arrows). (E) Boy aged 2 years with probable tuberculous meningitis: T2-weighted axial imaging of a child with signal abnormality and cystic and multinodular changes (arrow heads) along the inferomedial surface of the frontal lobes, temporal lobes, and cerebellar sulci, suggestive of pial involvement. (F) Boy aged 7 years with cerebral malaria: sagittal T1 showing diffuse cortical oedema with descent of the cerebellar tonsils (arrow). (G) Boy aged 6 years with cerebral malaria with bilateral T2 hyperintensity involving the basal ganglia. (H) Girl aged 11 years with non-typhoidal salmonella meningitis. Axial T2 (left) and sagittal T1-weighted (right) images showing hydrocephalus with moderate lateral ventricular dilatation, periventricular oedema, and mild dilatation of the third and fourth ventricles. (I) Boy aged 1 year with *Streptococcus pneumoniae* meningitis showing complicating bilateral subdural collections on the axial T2-weighted image. (J) Girl aged 4 years with *S pneumoniae* meningitis. Axial T2 (left), axial diffusion b900 (upper middle), and coronal FLAIR (lower middle) sequences with multifocal infarction (white arrows) involving the pons, midbrain, and right basal ganglia likely related to basal meningitis and vasculitis. There is evidence of hydrocephalus likely related to periaqueductal oedema (black arrow). (K) Boy aged 10 years with *S pneumoniae* meningitis: axial T2-weighted images show acute changes of cerebral cortex, left parietal, and right frontal cortex and subcortex, right lentiform nucleus with marked oedema and midline shift, left lentiform nucleus, thalamus extending to corona radiata. ADEM=acute disseminated encephalomyelitis. FLAIR=fluid-attenuated inversion recovery.

those with cerebral malaria alone (18 [67%] of 27 *vs* 11 [7%] of 154; p<0·0001; appendix 4 pp 47–48).

During hospital admission, a significantly higher proportion of children with non-malarial coma received intravenous antibiotics (114 [94%] of 121 *vs* 94 [41%] of 231; p<0·0001) and antiepileptics (65 [54%] of 121 *vs* 90 [39%] of 231; p=0·0080) than children with cerebral malaria. Not all children with cerebral malaria with a bacterial co-infection received intravenous antibiotics because molecular bacterial diagnosis was retrospective. In children with cerebral malaria and CNS bacterial co-infection, mortality was significantly higher among those who did not receive intravenous antibiotics (eight [57%] of 14) compared with those who did (one [10%] of 10; p=0·033). Mortality might

have been increased in all bacterial co-infections if antibiotics were not given in all cases (11 [39%] of 28 who did not receive intravenous antibiotics *vs* two [10%] of 21 who did receive intravenous antibiotics; p=0·053; appendix 4 p 49). Most children who died from cerebral malaria and bacterial co-infection did not receive intravenous antibiotics (11 [79%] of 13 [appendix 4 p 50]).

Mortality was significantly higher in the non-malarial group than the cerebral malaria group at 30 days (28 [24%] of 118 *vs* 33 [15%] of 223; p=0·041) and 180 days (32 [28%] of 114 *vs* 37 [18%] of 209; p=0·030; appendix 4 p 51), as were severe neurosequelae (Liverpool Outcome Scale score of 2) at 180 days (19 [17%] of 114 *vs* 15 [7%] of 209; p=0·0079), but both groups had neurosequelae (of any degree) in half of survivors at 180 days (table 2). Children with cerebral malaria and cerebrospinal fluid co-infection had significantly higher mortality than those with cerebral malaria alone (p=0·0033; table 1, figure 4, appendix 4 p 53). Survivors of cerebral malaria were more likely to have hearing loss at 180 days than survivors of non-malarial coma (four [3%] of 119 *vs* four [9%] of 47; p=0·0018; appendix 4 p 55).

A multivariable logistic regression model identified that a deeper level of coma—per BCS level increase (adjusted odds ratio [aOR] 0·45 [95% CI 0·29–0·73]), tachycardia (1·09 [1·01–1·17]), deep acidotic breathing (2·6 [1·17–6]), hyperlactataemia (1·09 [1·02–1·18]), raised cerebrospinal fluid opening pressure (1·04 [1–1·07]), abnormal cerebrospinal fluid profile (2·55 [1·2–5·4]), and a diagnosis of cerebral malaria and CNS co-infection (3·09 [1·08–8·7]), or septic encephalopathy (4·9 [1·1–21·8])—were significantly associated with death (appendix 4 pp 57–58). A separate multivariable logistic regression identified that being severely malnourished (3·05 [1·21–7·70]), HIV positivity (4·4 [1·06–18·4]), having meningitis (7·37 [1·44–37·60]), and a longer duration of fever (1·01 [1·00–1·01]) were significantly associated with long-term neurosequelae (appendix 4 pp 59–60).[26] We also examined a published model, combining clinical subgroups of deeper coma, acidotic breathing, and anaemia, developed for severe malaria.[26] The clinical subgroups were cumulative risk factors of all-cause febrile coma mortality, as well as cumulative risk factors for cerebral malaria mortality (appendix 4 pp 63–65).

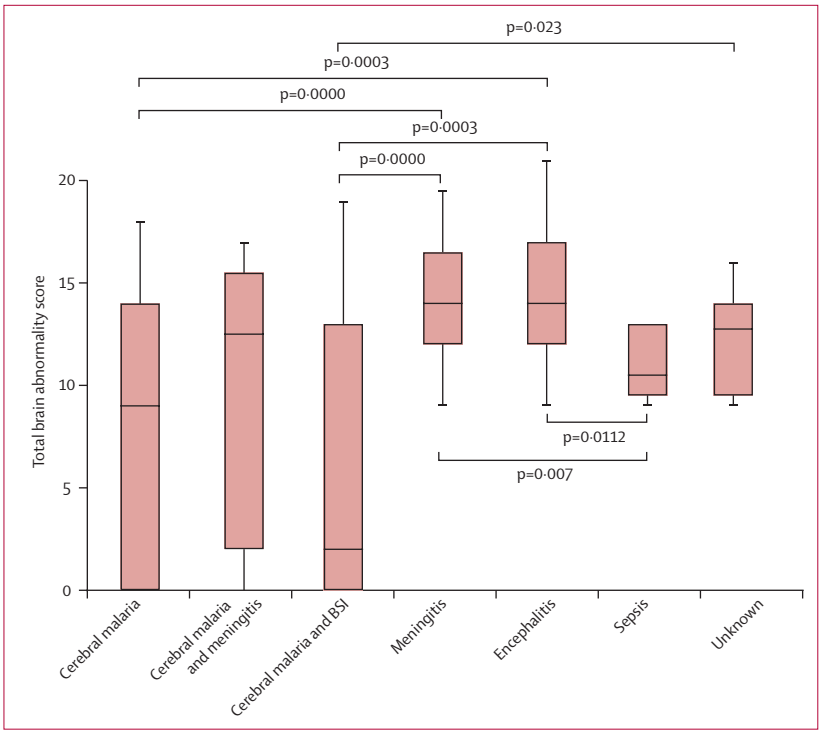

Figure 3: **Box plot of total brain abnormality score, by disease**
Box plots indicating the score for brain abnormality in each identified disease. Box midline shows the median score, ends of the boxes show the IQR, and the whiskers denote any outliers. Any abnormality in any of the following anatomical regions (irrespective of MRI sequence, total number of abnormalities, or whether unilateral or bilateral for that anatomical region) gets a score of 1 (normal 0, maximum score 26): ventricle abnormality (any); hydrocephalus; periventricular white matter hyperintensity; extra axial CSF spaces abnormal signal; cerebral cortex: frontal lobe, parietal lobe, temporal lobe, occipital lobe; basal ganglia: caudate, globus pallidus, putamen, thalamus; corpus callosum: genu, body, splenium, rostrum, cerebellum; brainstem: midbrain, pons, medulla; meningeal enhancement; venous flow void; arterial flow void; mastoids; paranasal sinuses; or orbits. BSI=bloodstream infection.

Discussion

To our knowledge, this is the first prospective cohort study performing neurological imaging, pathogen-specific PCR, and long-term neurodisability assessments among children with febrile coma in sub-Saharan Africa.

	All	Cerebral malaria (all)	Non-malarial coma (all)	Cerebral malaria *vs* non-malarial coma, p value	Cerebral malaria monoinfection	Cerebral malaria and meningitis	Cerebral malaria monoinfection *vs* non-malarial coma, p value
Death (LOS 1)	69/323 (21%)	37/209 (18%)	32/114 (28%)	<0·0001	23/143 (16%)	10/25 (40%)	0·0055
Any disability (LOS 2–4)	163/323 (50%)	106/209 (51%)	57/114 (50%)	0·92	78/143 (55%)	9/25 (36%)	0·13
Severe impairment (LOS 2)	34/323 (12%)	15/209 (7%)	19/114 (17%)	0·0079	13/143 (9%)	0/25	0·22
Moderate impairment (LOS 3)	54/323 (17%)	34/209(16%)	20/114 (18%)	0·77	22/143 (15%)	3/25 (12%)	>0·99
Mild impairment (LOS 4)	75/323 (23%)	57/209 (27%)	18/114 (16%)	0·020	43/143 (30%)	6/25 (24%)	0·64
No impairment (LOS 5)	91/323 (28%)	66/209 (32%)	25/114 (22%)	0·066	42/143 (29%)	6/25 (24%)	0·64

Data are n (%). p values correspond to differences between cerebral malaria and non-malarial coma groups across categories of impairment. Significance calculated using χ^2 testing. The reduction in total participants (denominator) within cohort proportions over time is owing to participants lost to follow-up or withdrawn from the study. LOS=Liverpool Outcome Scale.

Table 2: **Clinical outcome on the Liverpool Outcome Scale for all children with febrile coma followed at 180 days in the study**

We identified a range of causes of coma beyond malaria. PCR significantly increased pathogenic non-malarial diagnoses, including co-infection in more than a quarter of children with clinically diagnosed cerebral malaria. Co-infection prevalence was similar irrespective of malaria retinopathy. MRI revealed a high frequency of brain abnormalities, including surgically amenable complications in meningitis. Outcomes, including disability, were universally poor. Non-malarial coma and cerebral malaria with a co-infection had poorer outcomes than cerebral malaria alone.

We identified a pathogen by PCR or parasitology in more than 80% of children. PCR supported pathogen diagnosis in more than two thirds of children with meningitis, and we revealed a high burden of bacterial co-infection alongside cerebral malaria, despite frequent antibiotic exposure before sampling and late presentation to hospital (table 1). The high diagnostic yield in our study is likely, in part, due to timely sampling (eg, immediate lumbar puncture on admission), high volume collection, and prompt transfer for freezer storage. Work in high-income settings has shown the clinical benefits of PCR diagnostics in children,[27] but comparable work in sub-Saharan Africa is scarce.[28] The WHO Defeating Meningitis recommendations encourage introduction of molecular tools to improve diagnosis of CNS infections in sub-Saharan Africa.[10] Although access to molecular diagnostics has historically been limited, rapid implementation of COVID-19 PCR diagnostics during the pandemic highlights the feasibility of scale-up of such tools in sub-Saharan Africa.[31] In our study, pathogen-specific quantitative PCR identified pneumococcus most commonly, followed by *Salmonella* spp; these findings reflect earlier epidemiological studies, including those undertaken in Malawi, which have found that most invasive bacterial disease is caused by a few common pathogens.[32,33] Rational PCR panel selection could simplify scalability of molecular testing in sub-Saharan African hospitals.

More than 90% of admission MRI imaging revealed parenchymal abnormalities. CNS complications were substantially more frequent and extensive in patients with meningitis (both meningitis and meningitis co-infection with cerebral malaria) than in those with cerebral malaria alone, reflecting the higher mortality in those with meningitis (either alone or as a co-infection). The high burden of hydrocephalus and paranasal or subdural collections complicating meningitis were considerably more frequent than have previously been reported in high-income settings,[29,30] and these findings suggest that early surgical intervention might improve outcomes for these children in sub-Saharan Africa. Imaging also facilitated clinically unappreciated causes of febrile coma such as neurocysticercosis. Our study illustrates that neuroimaging at admission can support syndromic classification and identification of cerebral complications.

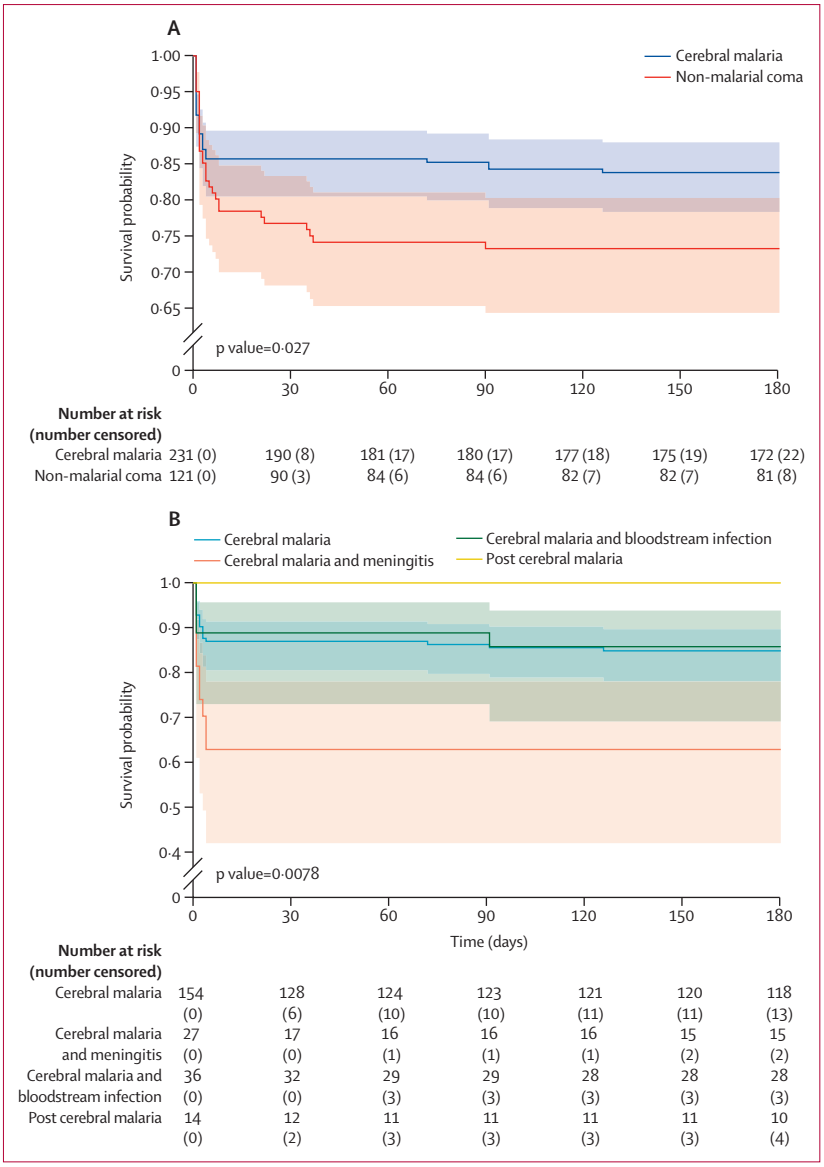

***Figure 4*: Kaplan–Meier survival curves of all children stratified by primary disease groups (A) and of all children with cerebral malaria by subgroup (B)**

Very limited numbers of fixed magnet scanners and radiologists in LMICs compared with high-income settings makes the scalability of equipment and expertise challenging.[31] Alternative imaging approaches are being investigated, including low-field, lower cost, portable MRI scanners, with cloud-based remote reporting.[32]

The proportion of bacterial co-infection within cerebral malaria is higher in our study than previous reports using routine culture only.[33] However, our data support local post-mortem data evidencing a considerable burden of meningitis co-infection in clinical cerebral malaria,[34] plus recent modelling analyses showing undiagnosed non-malarial causes of illness in up to a third of children diagnosed with severe malaria.[6–8,34]

It is plausible that some pathogens detected in our cohort were contaminants or molecular false positives. However, the pathogens detected in CNS infections were often accompanied by other confirmatory laboratory features, such as cerebrospinal fluid pleocytosis and abnormal biochemistry. Secondly, the predominant bacterial pathogens detected by PCR reflect those found in local microbiological surveillance.[35,36] Finally, the PCR-identified cerebral malaria and CNS co-infection group had a higher mortality rate than the group of children with cerebral malaria alone; deaths were even more common in those with cerebral malaria and CNS co-infection who did not receive intravenous antibiotics than in those who did. When malarial retinopathy is identified to support cerebral malaria diagnosis, antimicrobials are sometimes withheld in the absence of other clinical features of bacterial co-infection.[37] In our cohort, presence of retinal changes did not distinguish between cerebral malaria with versus without bacterial co-infection. Two previous viral co-infection studies have shown no relationship between retinopathy and CNS co-infection in cerebral malaria.[1,38]

Our study showed that no clinical symptoms or signs reliably distinguish cerebral malaria alone from cerebral malaria with a co-infection or non-malarial coma at admission. Neck rigidity was significantly more frequent in non-malarial coma but was only present in 12% of this non-malarial cohort (all cases were bacterial meningitis). Therefore, although it could be a useful feature to rule in meningitis, it is sufficiently infrequent as a sign that it cannot be used to differentiate between aetiologies (contrary to conventional wisdom that meningism is a common feature of bacterial meningitis). Furthermore, blood tests, including CRP, did not distinguish bacterial infection from other causes, nor did they aid identification of cerebral malaria with bacterial co-infection. Molecular diagnostics and neuroradiology in this study facilitated important disease classifications, improving epidemiology estimates of febrile coma pathogen and disease prevalence. In hospitals without enhanced research diagnostic capacity, very few of the co-infections we reported alongside cerebral malaria would have been identified, and most non-malarial coma cases would be syndromically classified as meningoencephalitis.

Childhood febrile coma is a life-threatening presentation that warrants immediate intervention. With no reliable clinical or laboratory features to differentiate cerebral malaria alone from cerebral malaria with bacterial co-infection, our findings further advocate for Integrated Management of Childhood Illness and WHO guidance to administer immediate parenteral antimicrobials and artesunate in children with severe malaria and altered consciousness.[39,40] We believe this guidance should be adhered to irrespective of retinopathy status. We estimate this approach could save the lives of more than 20 000 children across the African continent with cerebral malaria and bacterial co-infection per year (appendix 4 pp 61–62). Important limitations to this estimate are that assumptions are made that malaria transmission, the proportions of children with bacterial co-infection, and the proportion of children receiving antibiotics would be consistent across the continent. We also did not model the influence of malaria vaccine rollout, climate change, or health-care presentation in our estimates. The primary data for this model are derived from our single-site observational study (not a randomised trial). The co-infection prevalence and increased mortality we report are consistent with prior estimates[7] and our paired meta-analysis.[41] Cerebrospinal fluid pleocytosis was considerably more frequent in children with cerebral malaria and CNS co-infection than those with cerebral malaria alone, highlighting the importance of lumbar puncture in supporting the diagnosis of meningitis. Although peripheral white cell count was substantially higher in children with cerebral malaria and CNS co-infection than in those with cerebral malaria only, the overlapping IQRs make establishing a clear threshold for bacterial co-infection challenging. The findings of very low pathogen yield by routine culture underscores the importance of reliable diagnostic approaches for bacterial co-infection, such as molecular diagnostics. There is a need for pragmatic yet evidence-based rationalisation of antibiotics in febrile coma, a global priority with the explosion of antimicrobial resistance reported across sub-Saharan Africa.[36] In settings with restricted microbiological diagnostics, use of simple laboratory measurements, if available, could help guide duration of antibiotics in children with a clinical diagnosis of cerebral malaria. However, further work is needed to identify patients in whom it is safe to discontinue antibiotics at 48 h microbiology review. We found that long-term outcomes (180 days post-hospital discharge) for survivors were universally poor. Rates of death and severe neurological impairment in children with non-malarial coma were significantly higher than in those with cerebral malaria alone. Any degree of neurological impairment was present in approximately half of all survivors. Long-term neurological sequelae following cerebral malaria was more frequent than that seen in earlier estimates (see paired meta-analysis).[41] The observed low burden of hearing loss in children with cerebral malaria (four [3%] of 118) and moderate burden in meningitis (four [9%] of 47) is comparable to previous estimates.[42] Severely ill children presenting to African hospitals often have a constellation of clinical abnormalities.[43] One of our multivariable regression models reiterated that febrile coma patients are a complex and critically unwell cohort: deeper coma, acidotic breathing, hyperlactataemia, tachycardia, raised intracranial pressure, abnormal cerebrospinal fluid profile, cerebral malaria and meningitis dual infection, and septic encephalopathy are all independent predictors of mortality. Another of our analyses identified that baseline high-burden comorbidities (including severe malnutrition and HIV positivity), a diagnosis of

meningitis, and longer duration of fever all predict long-term neurosequelae from febrile coma.

Additionally, we found by post-hoc analysis that the published cumulative mortality model of clinical subgroups of severe malaria (severe coma, acidotic breathing, and anaemia) are also cumulative factors for increased mortality in all-cause febrile coma in addition to cerebral malaria in our cohort (appendix 4 pp 63–65).[26] The clinical severity of illness (severe coma, metabolic acidosis, and anaemia) and our findings of multiple brain imaging abnormalities on admission re-emphasises the need for early referral to hospitals with appropriate specialist care. Integrated Management of Childhood Illness guidelines state that febrile children with such danger signs should be referred to specialist hospital care immediately. However, in practice, referral remains a great challenge (eg, delayed presentation, limited diagnostics and treatment resources, and organisational barriers and lack of established referral pathways).

This study has several limitations. First, recruitment was from a single centre because it had a high-dependency unit and MRI facility where detailed research could be safely conducted on a critically unwell cohort of children with febrile coma. Second, 174 (49%) of 352 children did not undergo MRI due to an unexpected scanner breakdown, which was exacerbated by the COVID-19 pandemic. Third, despite predefined and peer-reviewed aetiological classification, diagnostic misclassification remains a risk with substantial clinical overlap. This risk is particularly true between septic encephalopathy, meningitis, and encephalitis, and it is compounded by limitations in microscopy and culture.

Despite malaria control efforts, cerebral malaria remains the most common cause of febrile coma in Malawi. However, non-malarial coma contributes a greater disease burden, with higher mortality and severe disability rates. To our knowledge, this is the first time that non-malarial co-infection has been identified in more than a quarter of children with cerebral malaria. Both non-malarial coma and cerebral malaria with co-infection were associated with a worse mortality rate than cerebral malaria alone. Commencing empirical antimicrobials to all children with febrile coma, including those with clinical cerebral malaria, could and should be rapidly implemented across Africa and must be considered.

This study also highlights the value of molecular diagnostics and the use of imaging to support diagnosis. The frequent brain abnormalities we found by imaging, including surgically amenable neurological complications, emphasises the requirement for earlier escalation (and access) to specialist care. Further work is needed to develop feasible molecular and radiological diagnostics for their successful deployment across the continent. Implementation of these methods might improve the diagnosis and poor outcomes for children with febrile coma in Africa.

Contributors

STJR, KS, and MJG led the design and conduction of the study. DGL, CAM, TT, YC, and CEF made substantial contributions to these aspects. AA led the acquisition, processing, analysis, and storage of laboratory samples. RB, JC, CA, MN, JR, CA, JF, and TP contributed to conduction and interpretation of the molecular diagnostic laboratory work. STJR, KS, TT, YC, AM-L, AM, AT, PP, MBG, DGP, NO, CEF, and JL made substantial contributions to the acquisition of clinical data. EK, AM, ES, AB, STJR, and CEF contributed to the acquisition of and management of the neurodevelopment data. RD and KC led the expert interpretation of MRI brain imaging. CC and SA substantially contributed to the MRI data collection and interpretation, respectively. DGP and GLB led data interpretation of the EEG. STJR, CEF, KS, and MJG led verification of the data. STJR analysed the data and prepared tables and figures, with support from MYRH. The manuscript was drafted by STJR, CEF, and MJG. STJR, CEF, MJG, KS, DGL, CAM, TT, GLB, BDM, TS, MG, SBG, and MYRH substantially contributed to the interpretation of the data and commented on the manuscript. All authors have read and approved the final manuscript. All authors had full access to all the data reported in this study and had final responsibility for the decision to submit for publication.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 5). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health's* broader goal to decolonise global health.

See **Online** for appendix 5

Declaration of interests

DGL, MYRH, CA, and SBG are supported by The Wellcome core award (award number 206545/Z/17/Z) to Malawi–Liverpool Wellcome Trust. STJR and MN are also supported by Wellcome to conduct paediatric infectious diseases research (203919/Z/16/Z). STJR is also supported by a Thrasher child health early career award, Academy of Medical Sciences starter grant, and European Society of Paediatric Infectious Diseases Society diagnostic grant; is a Centre for Human Genetics Well Institute Olink-48 grant prize winner and Early Career Research committee member, both at The University of Oxford. MN is also supported by Roche Diagnostics for a Baby and Mother Biomarkers of Infection study, Liverpool School of Tropical Medicine as a Clinical Fellow for The DIAMONDS Research Consortia, and FIND Diagnostics for a Literature review on the Utility of CRP testing in primary care in low-resource settings for supporting patient management and antibiotic stewardship; is an invited speaker at The Paediatric Infectious Diseases Games; and is Deputy Convenor, Research Co-Lead, and Winter Meeting Lead for the Royal College of Paediatrics and Child Health International Child Health Group. MJG is supported to conduct neuroscience and infection research internationally by the Medical Research Council (MRC) Newton Fund (MR/S019960/1), MRC Development Pathway Funding Scheme (MR/R015406/1) and National Institute for Health and Care Research (NIHR; 153195 17/60/67, 126156 17/63/11, and 200907). CAM is a UKRI MRC Future Leaders Fellow (MR/V025856/1). TS is supported by the NIHR Health Protection Research Unit in Emerging and Zoonotic Infections (IS-HPU-1112–10117), NIHR Global Health Research Group on Brain Infections (17/63/110), and The Pandemic Institute, Liverpool, UK; receives royalties from Oxford University Press, Liverpool University Press, Cambridge University, and Elsevier for published books he has written on brain infections; co-chaired the Medicines and Healthcare Products Regulatory Agency (MHRA) Expert Working Group on COVID-19 vaccines between 2020 and 2023; was a member of the COVID-19 Vaccines Benefit Risk Expert working group, for the Commission on Human Medicines (CHM) committee of the MHRA between 2020 and 2023; is a committee member of the Wellcome Trust Pathogen Biology and Disease Transmission Discovery Advisory Group; was a member of the MRC's Infections and Immunity Board between 2018 and 2022; sat on the Research Excellence Framework Panel between 2021 and 2022; and was on the Data Safety Monitoring Committee of the GSK Study to Evaluate the Safety and Immunogenicity of a Candidate Ebola Vaccine in Children (ChAd3 EBO-Z) vaccine (GSK3390107A). BDM is supported for COVID-19 neuroscience research by UK Research and Innovation (UKRI; MR/V03605X/1) and the MRC

(MR/V03605X/1); and for additional neurological inflammation due to viral infection research by grants from the MRC and UKRI (MR/V007181/1), MRC (MR/T028750/1), and the Wellcome Trust (ISSF201902/3). TT is supported by a research grant from the National Institutes of Health (NIH); is the President-Elect for the American Society of Tropical Medicine and Hygiene and is a member of the Malaria Advisory Council for Novartis. GLB is supported by two active and two recent research grants from NIH; consults on educational materials for Neurotorium, and TempTraq and similar devices at Blue Spark Technologies; lectures for The University of Calgary; participates on an advisory board for the BRIDGE clinical trial; and is on the editorial board of the *Lancet Neurology*, Neurotorium, and Zambian League against Epilepsy. RD is a consulting radiologist for a separate infection project for the University of Oxford; is an honorary teaching fellow at The Liverpool School of Tropical Medicine; is training programme advisor at the British Society of Head and Neck Imaging; examiner for The Royal College of Radiologists; and trustee and educational lead for Worldwide Radiology. STJR, BDM, and TS are members of the Encephalitis International Scientific Advisory Panel; BDM is Scientific Chair and TS is President. All other authors declare no competing interests.

Data sharing

Data can be requested from SJR and CF after publication of this study. De-identified participant data, data dictionary, and other specified datasets can be requested. The study design, including the statistical analysis plan is within this manuscript and associated appendix 4. Specific requests for data will require the submission of a proposal with a valuable research question as assessed by the study team. A data access agreement should be signed.

Acknowledgments

This study was funded by the Wellcome Trust (Clinical PhD Fellowship, University of Liverpool [203919/Z/16/Z]). We thank the patients, their families, and the staff at Queen Elizabeth Central Hospital, the Malawi–Liverpool Wellcome laboratory teams, and both the Blantyre Malaria Project and Malawi–Liverpool Wellcome data teams. We are indebted to the wondrous research nurses who cared for these critically unwell children. We would like to thank Bardatin Afia for her extensive work in the optimisation of these molecular pathogen targets in a LMIC. We would also like to thank Andrew Pollard and Dominic Kelly for supporting the development of this research beyond the PhD fellowship.

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