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Risk Factors for Death and Severe Sequelae in Malawian Children with Bacterial Meningitis, 1997--2010

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Abstract

Background—Acute bacterial meningitis causes significant death and disability in children worldwide, with HIV recognized as an established risk factor for infection and negative outcomes. However, additional major risk factors for death and disability in pediatric acute bacterial meningitis remain unclear.

Methods—We conducted a retrospective analysis of case data from three departmental studies of acute bacterial meningitis involving 1,784 children <15 years old who attended Queen Elizabeth Central Hospital in Blantyre, Malawi during 1997--2010. Univariate and multivariate logistic regression models were used to estimate the effects of HIV seropositivity, impaired consciousness, and causative organism on death and severe sequelae.

Results—Impaired consciousness or coma at the time of admission was strongly associated with death [Coma: OR = 14.4, 95%CI (9.42, 22.1)] and severe sequelae [Coma: OR = 3.27, 95%CI (2.02, 5.29)] in multivariate logistic regression models. HIV seropositivity was significantly associated with increased odds of death [OR = 1.65, 95%CI (1.20, 2.26)] but not with developing severe sequelae [OR = 0.88, 95%CI (0.56, 1.38)]. After adjustment, infection with *Salmonella* spp was associated with increased odds of death [OR = 2.11, 95%CI (1.06, 4.08)] and pneumococcal meningitis was associated with increased odds of severe sequelae [OR = 1.84, 95%CI (1.03, 3.29)].

Conclusions—Impaired consciousness and HIV infection increase the odds of death from ABM in Malawian children. Use of the pneumococcal conjugate vaccine could greatly reduce the burden of ABM in Malawi.

Keywords

Streptococcus pneumoniae; pediatric; impaired consciousness; bacterial meningitis; Malawi

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Introduction

Acute bacterial meningitis (ABM) is a major cause of death and morbidity in children worldwide.[1-3] *Neisseria meningitidis, Streptococcus pneumoniae,* and *Haemophilus influenzae* type b (Hib) cause most ABM in children. The case-fatality ratio (CFR) is approximately 90% for untreated cases of pneumococcal and Hib meningitis, and the CFR following treatment is higher in children in resource-limited countries compared to industrialized countries.[1,2] ABM also causes disabling sequelae (e.g. hearing loss, motor deficit, visual impairment) in one-quarter of pneumococcal meningitis cases and one-tenth of Hib meningitis cases.[4] Permanent sequelae are more common in Africa and Southeast Asia than in Europe and North America, and afflicted children often face discrimination and decreased quality of life.[5,6] Children infected with the human immunodeficiency virus (HIV) are at higher risk of ABM and resulting mortality.[1,2,7-9] This disparity in mortality is particularly pronounced for children with pneumococcal meningitis.[8,9]

Malawi is one of the world's poorest countries with a per capita GDP of US$190/year. The average life expectancy at birth is 40 years (yr) and ~15% of the adult population and ~1.4% of children are infected with HIV.[10,11] Pneumococcal and Hib meningitis account for most cases of ABM in Malawi, although the prevalence of Hib meningitis decreased dramatically following the introduction of the conjugate Hib vaccine in 2002. Meningococcal meningitis is rare.[3,12-14] To investigate factors related to mortality and severe sequelae in Malawian children with ABM during 1997--2010, we performed a retrospective database review of three ABM clinical trials conducted during that time period.

Methods

Study Location

Queen Elizabeth Central Hospital (QECH) is a major referral center serving the southern region of Malawi and is the district hospital for Blantyre District. There are 180 pediatric beds, but the average number of inpatients is 280-350. Approximately 23,000 children are admitted annually, including ~400 cases of ABM (~3% of all pediatric admissions).[15]

Study Population

Hospital records of 1,784 children (<15 yr) with ABM enrolled in three ABM studies at QECH from July 1997 through June 2010 were reviewed. Data from three clinical trials evaluating treatment regimens for bacterial meningitis were used: Study 1,[15] which assessed dexamethasone as adjuvant therapy (July 1997--October 2000),Study 2,[16] which compared 5 v. 10 days of ceftriaxone treatment (October 2001--December 2007), and Study 3, an ongoing study assessing glycerol adjuvant therapy (January 2008--June 2010). Further recruitment details are presented elsewhere.[15] Briefly, all children ≥2 months of age with suspected ABM who presented to the QECH Admitting and Emergency Ward were eligible to participate and those whose parents provided assent were recruited. The participation rate was high (>90%) for all studies and most refusals were due to concern regarding HIV testing.

Case Definition

ABM was defined as ≥100 white cells per high-power field, or a positive culture or Gram stain from an admission sample of CSF. Children who received any parenteral broad-spectrum antibiotic within 24 hours of admission and cases of tuberculosis meningitis were excluded.

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Clinical and Laboratory Procedures

After obtaining verbal assent from the child's parent or guardian in their native language, a complete history and physical exam was performed. Blood samples were taken on admission for full blood count, thick film blood smear, and blood culture. Participants were classified as parasitemic (*Plasmodium* parasites visible on thick film blood smear) or aparasitemic (no *Plasmodium* parasites visible).

Unless contraindicated, a lumbar puncture was collected aseptically on admission before administration of antibiotics. Cerebrospinal fluid (CSF) specimens were cultured directly onto blood and chocolate agar plates and into brain heart infusion (BHI) broth and incubated at 37°C for 48 hours. If no growth was observed on the agar plates after 48 hours, the BHI was centrifuged and the pellet was collected and cultured onto fresh blood and chocolate agar plates and incubated for an additional 48 hours. Isolates were identified using standard procedures. Before BHI was used routinely (Study 1), if no organisms were observed by culture or microscopy after two days, the CSF specimens were tested for five common microorganismal antigens (Hib, *S. pneumoniae, N. meningitidis*, Group B *Streptococcus*, and *Escherichia coli*) using latex agglutination reagents (Murex, Kent, UK, MAST Group, Merseyside, UK) according to the manufacturers' instructions.

For HIV, serum samples were tested using at least two antibody-based rapid diagnostic tests. Discordant tests were confirmed using a third antibody-based rapid diagnostic test. Children <18months (mo) of age with a positive antibody test had their serostatus confirmed by PCR. Due to the long period of time over which samples were collected there were variations in CSF sample processing and the HIV rapid test used. Additional details are presented elsewhere.[15,16]

Description of Predictor Variables

The primary exposure of interest was the pathogenic microorganisms. Assessment of neurologic function, vision, hearing, and development were conducted prior to discharge. At discharge, participants were classified as "Alive; no permanent sequelae", "Alive; permanent sequelae", "Died", or "Alive; possible sequelae." Follow-up assessments were inconsistent across studies. To preserve analytic accuracy participants classified as having possible sequelae following their ABM episode were excluded from analyses comparing survivors who lacked long-term consequences to those who suffered long-term damage.

Anemia status was assessed by blood hemoglobin (Hb) levels. We obtained Hb measurements using a Coulter counter on venous blood samples. Children were categorized as not anemic (≥11.0 g/dL), mildly anemic (8.0--10.9 g/dL), moderately anemic (5.0--7.9 g/dL), and severely anemic (≤5.0 g/dL). Less than 5% of children were severely anemic and the categories of moderate anemia and severe anemia were combined to preserve statistical efficiency.

Delay in seeking medical treatment was assessed by the number of days that the parent reported a child was febrile prior to admission. Children with reported fever duration of more than 10 days (76/1769, 4.3% of total sample) were not considered in analyses examining fever duration to exclude cases of fever with an etiology unrelated to ABM.

Level of consciousness was determined on admission using the Blantyre Coma Score (BCS).[17] Children with a BCS of 5 were classified as "Fully Conscious," children with at BCS of 3--4 were classified as having "Impaired Consciousness," and children with a BCS ≤2 were classified as "Comatose."

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Weight of each participant was measured on admission using a digital scale (accuracy ±500 g), either with a pan for younger children or standing scale for older children. Nutritional status was defined by dividing the child's weight by the gender-specific median weight for that age (WHO Multicentre Growth Reference Study 50th percentile)[18] and multiplying by 100. Based on the resulting percentage, children were categorized as normal (≥100%), underweight (81--100%), malnourished (71--80%), wasted (61--70%), or severely wasted (≤60%). Multicentre Growth Reference Study data are only available for children aged 0--10 and consequently nutritional status was not determined for children older than 120 mo (n = 165, 9.2% of total sample).

Statistical Methods

Data were entered and cleaned using Excel (Microsoft Corp., Redmond, WA). All statistical analyses were carried out using Stata (v. 10.1 SE, Statacorp., College Station, TX). We used the two-tailed Z-test to compare dichotomous variables and proportions, the two-tailed t-test and Mann-Whitney U test to compare continuous variables, and the chi-square test to examine associations between categorical variables. If the expected cell count was less than five for these analyses, Fisher's Exact Test was used. An α value of ≤0.05 was considered significant.

Logistic regression was employed to investigate multivariable relationships. We constructed two separate multivariable logistic regression models to assess factors related to negative outcomes following treatment (death and permanent neurologic or hearing damage). One model compared all children with ABM who survived, irrespective of permanent sequelae, to those who died, while the other model compared survivors without permanent damage to those who suffered permanent neurologic or hearing damage. Participants who survived but whose status at discharge was unclear (n = 277, 22.1%) were not included in this second logistic regression model.

All variables of interest were first examined using a univariate model and based on these results multivariable models were constructed. Variables were selected for inclusion in the final multivariable model if the regression coefficient was significant at the 5% level or if they changed one or more of the other variables' parameter estimates by >10%.

Results

Demographics

There were 1,784 children with ABM at QECH during July 1997--June 2010. Six-hundred and one (33.7%) participated in Study 1[15] (July 1997--October 2000), 973 (54.5%) were in Study 2[16] (October 2001--December2007), and 210 (11.8%) were in Study 3 (January 2008--June2010, EM Molyneux, personal communication). Their ages ranged from 2 mo to 15 yr (median = 18 mo, IQR = 2--72 mo); 363 children (20.4%) were younger than 6 mo. The age distribution differed significantly across research studies (p< 0.0001, Table 1). Nine-hundred forty-nine children (53.5%) were male, a proportion that was similar across studies (p = 0.08).

Pathogens

Detailed information on causative organism was available for 1,773 children (99.4% of total sample; Table 2; a detailed organism breakdown is available upon request). The most common causative organisms were *S. pneumoniae* (884, 49.9%), Hib (323, 18.2%), and *N. meningitidis* (96, 5.4%). *Salmonella* spp caused 128 (7.2%) cases of ABM, and other organisms, including *Escherichia coli* and *Klebsiella* spp accounted for 86 (4.8%) cases. No microorganisms were cultured in 256 (14.4%) cases.

Information on HIV serostatus was available for 1,520 (85.2%) children, of whom 559 (36.8%) were HIV seropositive. HIV test results were equivocal for one child who was excluded from all analyses involving HIV serostatus. No significant differences were observed across studies in the proportion of HIV seropositive children ($p = 0.38$) (Table 1).

HIV seropositive were significantly older than seronegative children (29 mo vs. 14 mo, $p<0.0001$) (Table 3). Malnutrition, wasting, and severe wasting were significantly more common in HIV seropositive children. A significantly higher proportion of seropositive children were admitted in a comatose state (BCS ≤2), while *Plasmodium* infection was more prevalent in seronegative children. Pneumococcal meningitis accounted for a higher percentage of ABM in HIV seropositive children, while proportionally less meningococcal ABM was seen in seropositive children (Table 3).

Outcome at Discharge

Status at discharge was recorded for 1,762 children (98.8%). Of these, 517 (29.3%) survived with no permanent sequelae, 462 (26.2%) survived but suffered permanent sequelae, 278 (15.8%) survived with possible permanent sequelae, and 505 (28.7%) died. The proportion of children with severe sequelae was dramatically higher in Studies 2 and 3 compared to Study 1, and there was a corresponding decrease in the number of participants diagnosed as having survived with no long-term damage. The proportion of children who died remained relatively constant over the period of study (Chi-square goodness-of-fit test $p = 0.10$).

Death was more frequent among HIV seropositive children compared to seronegative children (36.9% vs. 25.4%; $p<0.001$) (Table 4). Children who died were significantly younger (median age 12 mo, IQR 6--60 mo) than those who survived (median age 21 mo, IQR 6--77) ($p=0.0003$), and a significantly higher proportion of girls died ($p=0.05$). Children who died were more likely to be anemic, have impaired consciousness (BCS 3--4), or be admitted in a comatose state (BCS ≤2). Malnutrition, wasting, and severe wasting were more common in children who died (Table 4). The CFR varied by organism as follows: pneumococcal meningitis 32.5%, Hib meningitis 26.2%, meningococcal meningitis 3.1%, salmonella-associated meningitis 43.2%, other infectious etiology 25.0%, and 22.0% in children from whom no species was identified (Table 4).

In univariate logistic regression models, factors associated with increased odds of death included HIV seropositivity, wasted and severely wasted nutritional status, moderate/severe anemia (Hb<8.0 g/dL), young age (<24 mo), infection with *S. pneumoniae* and *Salmonella* spp., and impaired consciousness (BCS ≤4) (Table 5). The odds of death following infection with *N. meningitidis* were approximately nine-fold lower than children from whom no culture was grown (OR = 0.11, 95%CI = 0.03--0.38). HIV seropositivity (OR = 1.65, 95%CI = 1.20--2.26) remained significantly associated with death after adjusting for additional risk factors. *Salmonella* spp infection (OR = 2.11, 95%CI = 1.06--4.08), impaired consciousness (OR = 4.00, 95%CI = 2.54--6.29) and coma (OR = 14.4, 95%CI = 9.42--22.1) strongly increased the odds of death in the fully adjusted model. Males had slightly lower odds of death (OR = 0.75, 95%CI = 0.56--1.01). Participants from the Study 2 and Study 3 had lower odds of death than those from Study 1 (Table 5).

Younger children (≤24 mo) had increased odds of severe sequelae following infection in both univariate and adjusted logistic regression models (Table 6). Although mild anemia (Hb 8.0--10.9 g/dL) and moderate/severe anemia (Hb<8.0 g/dL) were significantly associated with increased odds of developing permanent sequelae in univariate logistic regression models, this association was not significant after adjustment. A strong association between participating in Study 2 and developing permanent sequelae was observed after adjustment (OR = 5.04, 95%CI = 3.33--7.61). Children with *S. pneumoniae* and *Salmonella*

spp infection were at increased odds of developing permanent sequelae following treatment for ABM. Impaired consciousness and coma increased the odds of developing severe sequelae in both univariate and fully adjusted model (Table 6).

Discussion

This study is the first to examine major risk factors for death and severe sequelae for childhood ABM in a large sub-Saharan African cohort (>1,500) over the course of more than a decade. The CFR from ABM was high among this population in which pneumococcal meningitis represented the most frequent etiology, HIV prevalence was high, and severe sequelae following infection were common.

Impaired consciousness (BCS ≤4) on admission was the most important predictor of death and permanent sequelae in children with ABM. A recent study of Angolan children with ABM reported an increase in the odds of death and severe sequelae in children with a BCS ≤4; however, their analysis did not control for HIV infection.[19] Our study expands upon previous findings by examining the relationships between impaired consciousness, death, and severe sequelae using a larger study population and controlling for HIV and other additional risk factors. Our results support the growing body of evidence indicating that impaired consciousness on admission is an indicator of severe neuronal injury, which may be a major driver of the high ABM-associated mortality rates observed in resource-limited countries.[19-22]

Although malnutrition was not significantly associated with death in multivariate analysis, we observed a consistently positive OR that tended to increase with increasing degree of malnutrition in all models. This trend is highly suggestive of a positive association between malnutrition and death, particularly in the context of other studies that have reported such a link.[19,23,24] This lack of significance in our study may be due to insufficient sample size, reflected in the relatively broad confidence intervals. A recent study of ABM in Angolan children also found a weak non-significant association between death and both severe sequelae and poor nutritional status, lending support to the possibility that a small sample size may explain a lack of statistical significance.[19]

Young age (<24 mo) was consistently associated with negative outcomes, although this was not significant after adjustment. The confidence intervals were broad, suggesting that sample size may have been insufficient in multivariate models. In a recent review of mortality and severe sequelae predictors, young age (<24 mo) was a significant risk factor, but the quality of studies considered was variable and included both industrialized and resource-limited countries.[25] The differences in the outcome and presentation of childhood ABM between industrialized and resource-limited countries make it difficult to generalize from that review.[26] Our findings suggest that young age is an important independent risk factor, but further work is warranted.

Two previous studies of ABM in Malawian children also reported a weak protective effect for male gender on odds of death.[27,28] In contrast, a recent review concluded that male gender increased odds of death.[25] The observed association in our study may be due to residual confounding and we recommend further research.

Coma was more common in children with pneumococcal meningitis and less common in children with meningococcal meningitis, suggesting that the propensity of organisms to cause irreversible neuronal damage and induce coma/impaired consciousness may account for the differential mortality observed for different etiologic agents.

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A possible limitation of our study was that data were analyzed retrospectively and methods were not consistent over the time period that was analyzed. These differences in follow-up and diagnostic criteria are likely to account for the increased odds of permanent sequelae observed in children who had participated in Studies 2 and 3. By adjusting for the study in which children were diagnosed and treated, we minimized this potential bias. These studies did not overlap temporally, so they serve as a proxy for calendar time and changes in treatment. Treatment and diagnostic criteria were constant within each study.

HIV infection among children in developing countries is strongly associated with acquiring ABM and subsequent mortality.[29] Nearly two-thirds of children with pneumococcal meningitis were HIV seropositive compared to an estimated overall childhood prevalence of 1.4% in Malawi. A previous study estimated that 18.9% of all children admitted to QECH during March 2000 were HIV seropositive.[30] Seropositive children who required resuscitation on admission to QECH were significantly less likely to survive to discharge than seronegative children (56% vs. 79%), supporting an independent negative effect on mortality for HIV infection.[31] Seropositive children in our study were more likely to be admitted with impaired consciousness, although the reasons for this association are unclear and warrant further investigation.

We have shown that pneumococcal meningitis causes the majority of ABM and results in significant mortality and disability among children in Blantyre. The pneumococcal conjugate vaccine (PCV13) is effective against most major disease-causing *S. pneumoniae* serotypes, and its recent introduction in November 2011 should reduce the mortality and prevent long-term sequelae associated with pediatric pneumococcal meningitis.[32] This vaccine should also effectively reduce ABM in HIV-infected children.[33] Impaired consciousness and HIV infection are the leading risk factors for death and severe sequelae in childhood ABM in Malawi.

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Table 1

Association between study (Study 1: July 1997--October 2000; Study 2: October 2001--December2007; Study 3: January 2007--June2010) outcome at discharge, demographics, anthropometric data, and causative organism at Queen Elizabeth Central Hospital, Blantyre, Malawi. All *p*-values are in reference to Study 1 (used as the baseline).

	Study				
	Study 1 (*n* = 601)	**Study 2 (*n* = 973)**	***p*-value**	**Study 3 (*n* = 210)**	***p*-value**
Outcome (*n* = 1,762)					
Alive, no sequelae	418 (69.9)	684 (71.6)	0.47	155 (74.5)	0.18
Died	180 (30.1)	272 (28.5)	0.50	53 (25.5)	0.21
Age in Months (*n* = 1,779)					
<6	125 (20.8)	207 (21.3)	0.81	31 (14.8)	0.06
6-24	236 (39.3)	336 (34.6)	0.06	62 (29.7)	0.01
25-60	71 (11.8)	146 (15.1)	0.07	38 (18.2)	0.02
>60	168 (28.0)	281 (29.0)	0.67	78 (37.3)	0.01
Gender (*n* = 1,774)					
Female	261 (43.5)	462 (47.8)	0.10	102 (49.0)	0.17
Male	339 (56.5)	504 (52.2)	0.08	106 (51.0)	0.17
Nutritional Status (*n* = 1,606)[a]					
Normal	67 (12.3)	144 (16.4)	0.03	33 (18.0)	0.07
Underweight	215 (39.5)	308 (35.0)	0.07	74 (40.4)	0.82
Malnourished	144 (26.5)	234 (26.6)	0.97	40 (21.9)	0.19
Wasted	76 (14.0)	123 (14.0)	1.00	29 (15.9)	0.75
Severely Wasted	42 (7.7)	70 (8.0)	0.83	7 (3.8)	0.07
Anemia (Hb *g*/dL) (*n* = 1,427)					
No anemia (≥11.0)	92 (17.3)	107 (15.0)	0.23	42 (22.8)	0.10
Mild anemia (8.0--10.9)	217 (40.9)	311 (43.7)	0.28	86 (46.7)	0.17
Moderate/severe anemia (<8.0)	222 (41.8)	294 (41.3)	0.84	56 (30.4)	0.006
HIV serostatus (*n* = 1,519)[b]					
HIV seropositive	158 (34.2)	328 (38.0)	0.13	73 (37.4)	0.42
HIV seronegative	304 (65.8)	534 (62.0)	0.13	122 (62.6)	0.40
Level of Consciousness (*n* = 1,767)					
Fully Conscious (BCS = 5)	220 (36.7)	334 (34.8)	0.44	81 (38.9)	0.57
Impaired Consciousness (BCS 3--4)	169 (28.2)	253 (26.4)	0.44	66 (31.7)	0.34
Coma (BCS ≤2)	210 (35.1)	373 (38.9)	0.13	69 (29.3)	0.13
Causative Organism (*n* = 1,773)					
Streptococcus pneumoniae	229 (38.1)	550 (57.1)	<0.0001	105 (50.2)	0.002

	Study				
	Study 1 (*n* = 601)	**Study 2 (*n* = 973)**	***p*-value**	**Study 3 (*n* = 210)**	***p*-value**
Haemophilus influenzae type b	170 (28.3)	137 (14.2)	<0.0001	16 (7.7)	<0.0001
Neisseria meningitidis	64 (10.7)	28 (2.9)	<0.0001	4 (1.9)	0.0001
Salmonella spp	31 (5.2)	85 (8.8)	0.008	12 (5.7)	0.78
Other	29 (4.8)	37 (3.8)	0.34	20 (9.6)	0.01
No Growth	78 (13.0)	126 (13.1)	0.95	52 (24.9)	0.0001
***Plasmodium* Infection (*n* = 1,749)**					
Absent	502 (84.1)	886 (93.3)	<0.0001	189 (93.6)	0.0005
Present	95 (15.9)	64 (6.7)	<0.0001	13 (6.4)	0.0005
Median Duration of Hospital Stay (days, IQR) (*n* = 1,757)	10 (4--11)	11 (5--11)	0.02[†]	10 (5--10)	0.001[c]
Median Duration of Fever before Presentation (days, IQR) (*n* = 1,690)	3 (1--4)	3 (2--4)	0.01[†]	3 (2--4)	0.55[c]

[a] Nutritional status only assessed in children ≤10 years.

[b] HIV results were equivocal for one patient who was excluded from the analysis.

[c] *p*-value determined using Mann-Whitney U test.

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Table 2

Causative organism in children with acute bacterial meningitis, Queen Elizabeth Central Hospital, Blantyre, Malawi, 1997--2010 (*n* = 1,773).

Organism	*n* (%)
***Streptococcus* spp**	**904 (51.1)**
Streptococcus pneumoniae	884 (49.9)
Non-pneumococcal[a]	20 (1.1)
Haemophilus influenzae	**334 (18.8)**
type b	323 (18.2)
not type b[a]	11 (0.6)
Neisseria meningitidis	**96 (5.4)**
***Salmonella* spp**	**128 (7.2)**
Salmonella typhimurium	96(5.4)
Salmonella enteritidis	22 (1.2)
Salmonella spp, NOS	10 (0.6)
Other	**55 (3.1)**
Escherichia coli	8 (0.5)
Staphylococcus aureus	5 (0.3)
Gram-positive diplococci, NOS	18 (1.0)
Gram-negative rods, NOS	6 (0.3)
All Other[a]	18 (1.0)
No Growth	**256 (14.4)**

NOS = Not otherwise specified

[a]Further details available directly from the authors

Table 3

Univariate analysis of demographics, anthropometric data, and causative organism for children with acute bacterial meningitis by HIV serostatus, Queen Elizabeth Central Hospital, Blantyre, Malawi, 1997--2010.

	HIV Serostatus [n, (%)]		
	HIV Seropositive (*n* = 560)	**HIV Seronegative (*n* = 960)**	***p*-value**
Age in Months (*n* = 1,517)			
<6	86 (15.4)	233 (24.3)	<0.0001
6-24	176 (31.5)	346 (36.1)	0.07
25-60	101 (18.1)	116 (12.1)	0.001
≥60	195 (35.0)	264 (27.5)	0.002
Gender (*n* = 1,510)			
Female	281 (50.6)	435 (45.6)	0.06
Male	274 (49.4)	520 (54.4)	
Nutritional Status (*n* = 1,372)[a]			
Normal	45 (8.9)	169 (19.6)	<0.0001
Underweight	154 (40.3)	354 (41.0)	0.47
Malnourished	246 (28.7)	202 (23.4)	0.03
Wasted	104 (20.5)	99 (11.5)	<0.0001
Severely Wasted	59 (11.6)	40 (4.6)	<0.0001
Anemia (Hb *g*/dL) (*n* = 1,276)			
No anemia (≥11.0)	52 (12.0)	161 (19.1)	0.001
Mild anemia (8.0--10.9)	195 (44.9)	348 (41.3)	0.22
Moderate/severe anemia (<8.0)	187 (43.1)	333 (39.6)	0.23
Malaria Infection (*n* = 1,499)			
Absent	514 (93.3)	842 (88.8)	0.005
Present	37 (6.7)	106 (11.2)	
Causative Organism (*n* = 1,514)			
Streptococcus pneumoniae	356 (64.0)	412 (43.0)	<0.0001
Haemophilus influenzae type b	61 (11.0)	210 (21.9)	<0.0001
Neisseria meningitidis	7 (1.3)	58 (6.1)	<0.0001
Salmonella spp	37 (6.7)	77 (8.0)	0.36
Other	24 (4.3)	51 (5.3)	0.39
No Growth/NOS	71 (12.8)	150 (15.7)	0.12
Level of Consciousness (*n* = 1,513)			
Fully Conscious (BCS = 5)	164 (29.5)	366 (38.2)	0.0006
Impaired Consciousness (BCS 3--4)	170 (30.6)	259 (27.1)	0.14
Coma (BCS <2)	222 (39.9)	332 (34.7)	0.04
Median Duration of Hospital Stay (days, IQR) (*n* = 1,507)	11 (2--11)	11 (6--11)	0.01[b]
Median Duration of Fever before Presentation (days, IQR) (*n* = 1,446)	3 (2--4)	3 (2--5)	0.0002[b]

[a] Nutritional status only assessed in children ≤10 years.

[b] *p*-value determined using Mann-Whitney U test.

Table 4

Association between outcome at discharge, HIV serostatus, demographics, and anthropometric data. Queen Elizabeth Central Hospital, Blantyre, Malawi, 1997--2010.

	Outcome at Discharge		
	Alive (*n* = 1,257)	**Dead (*n* = 505)**	***p*-value**
HIV serostatus[a] (*n* = 1,511)			
HIV seropositive	351 (33.0)	205 (45.8)	<0.001
HIV seronegative	712 (67.0)	243 (54.2)	
Age in Months (*n* = 1,759)			
<6	248 (19.8)	113 (22.3)	0.10
6-24	417 (33.3)	209 (41.5)	0.001
25-60	198 (15.8)	54 (10.7)	0.006
>60	391 (31.2)	129 (25.5)	0.02
Sex (*n* = 1,754)			
Female	564 (45.1)	253 (50.2)	0.05
Male	686 (54.9)	251 (49.8)	
Nutritional Status (1,593)[b]			
Normal	183 (16.3)	60 (12.8)	0.08
Underweight	438 (39.0)	155 (33.1)	0.03
Malnourished	286 (25.4)	127 (27.1)	0.48
Wasted	145 (12.9)	80 (17.1)	0.03
Severely Wasted	72 (6.4)	47 (10.0)	0.01
Anemia (Hb g/dL) (*n* = 1,417)			
No anemia (≥11.0)	185 (18.3)	55 (13.5)	0.03
Mild anemia (8.0--10.9)	446 (44.2)	163 (40.0)	0.15
Moderate/severe anemia (<8.0)	378 (37.5)	190 (46.6)	0.002
***Plasmodium* Infection (*n* = 1,738)**			
Absent	1,123 (90.1)	444 (90.3)	0.94
Present	123 (9.9)	48 (9.7)	
Causative Organism (*n* = 1,757)			
Streptococcus pneumoniae	594 (47.4)	286 (56.9)	0.0003
Haemophilus influenzae type b	238 (19.0)	84 (16.7)	0.26
Neisseria meningitidis	93 (7.4)	3 (0.6)	0.30
Salmonella spp	71 (5.7)	54 (10.7)	0.0002
Other/NOS	63 (5.0)	21 (4.2)	0.48
No Growth	195 (15.6)	55 (10.9)	0.01
Level of Consciousness (*n* = 1,756)			
Fully Conscious (BCS = 5)	570 (45.5)	57 (11.4)	<0.0001
Impaired Consciousness (BCS 3--4)	370 (29.5)	116 (23.1)	0.007
Comatose (BCS ≤2)	314 (25.0)	329 (65.5)	<0.0001
Median Duration of Hospital Stay (days, IQR) (*n* = 1,752)	11 (10--11)	1 (1--3)	<0.0001[a]
Median Duration of Fever before Presentation (days, IQR) (*n* = 1,678)	3 (2--4)	3 (2--5)	0.66[a]

[a] *p*-value determined using Mann-Whitney U test.

[b] Nutritional status only assessed in children ≤10 years.

Table 5

Univariate and multivariate logistic regression models of the association between HIV serostatus, anthropometrics, demographics, and causative organism on death in children with acute bacterial meningitis, Queen Elizabeth Central Hospital, Blantyre, Malawi, 1997--2010.Alive is used as the reference group.

	Unadjusted Model [OR, (95%CI)][a]	First Adjusted Model [OR, (95%CI)][b]	Second Adjusted Model [OR, (95%CI)][c]
HIV Serostatus (*n* = 1,511)			
Negative	Ref	Ref	Ref
Positive	**1.71 (1.37, 2.14)**	**1.76 (1.30, 2.39)**	**1.65 (1.20, 2.26)**
Nutritional Status (*n* = 1,593)[d]			
Normal	Ref	Ref	Ref
Underweight	1.08 (0.76, 1.52)	1.20 (0.77, 1.87)	1.21 (0.77, 1.90)
Malnourished	1.35 (0.95, 1.94)	**1.58 (0.98, 2.54)**	**1.64 (1.01, 2.67)**
Wasted	**1.68 (1.13, 2.51)**	1.52 (0.88, 2.61)	1.57 (0.91, 2.73)
Severely Wasted	**1.99 (1.25, 3.18)**	**1.87 (0.96, 3.63)**	1.78 (0.90, 3.50)
Anemia (Hb g/dL) (*n* = 1,417)			
No anemia (≥11.0)	Ref	Ref	Ref
Mild anemia (8.0--10.9)	1.23 (0.87, 1.75)	0.94 (0.57, 1.53)	0.84 (0.51, 1.38)
Moderate/severe anemia (<8.0)	1.69 (1.19, 2.39)	0.94 (0.55, 1.60)	0.76 (0.44, 1.33)
Age in Months (*n* = 1,759)			
<6	**1.38 (1.02, 1.86)**	1.43 (0.88, 2.34)	1.38 (0.83, 2.27)
6-24	**1.52 (1.17, 1.97)**	1.26 (0.80, 1.99)	1.31 (0.82, 2.09)
25-60	0.83 (0.58, 1.19)	0.76 (0.47, 1.26)	0.79 (0.47, 1.31)
>60	Ref	Ref	Ref
Sex (*n* = 1,754)			
Female	Ref	Ref	Ref
Male	**0.82 (0.66, 1.00)**	**0.73 (0.55, 0.97)**	**0.75 (0.56, 1.01)**
Causative Organism (*n* = 1,757)			
Streptococcus pneumoniae	**1.71 (1.23, 2.38)**		1.10 (0.68, 1.79)
Haemophilus influenzae type b	1.25 (0.85, 1.85)		0.89 (0.51, 1.56)
Neisseria meningitidis	**0.11 (0.03, 0.38)**		NA[e]
Salmonella spp	**2.70 (1.70, 4.29)**		**2.11 (1.06, 4.08)**
Other/NOS	1.18 (0.66, 2.11)		0.61 (0.27, 1.42)
No Growth	Ref		Ref
Study (*n* = 1,762)			
Study 1	Ref	Ref	Ref
Study 2	0.92 (0.74, 1.16)	**0.67 (0.49, 0.91)**	**0.58 (0.42, 0.80)**
Study 3	0.79 (0.56, 1.14)	**0.60 (0.37, 0.98)**	**0.53 (0.32, 0.88)**
Level of Consciousness (*n* = 1,756)			
Normal	Ref	Ref	Ref
Impaired (BCS 3--4)	**3.14 (2.22, 4.42)**	**4.23 (2.71, 6.62)**	**4.00 (2.54, 6.29)**
Coma (BCS ≤2)	**10.5 (7.66, 14.3)**	**14.6 (9.62, 22.3)**	**14.4 (9.42, 22.1)**
Days of Fever (*n* = 1,678)	1.01 (0.96, 1.06)		
***Plasmodium* Infection (*n* = 1,738)**			
Absent	Ref		
Present	0.99 (0.69, 1.40)		

[a] Model contains only the variable of interest.

[b] Model mutually adjusted for HIV serostatus, nutritional status, anemia, age, sex, research study, and level of consciousness (n = 1,063).

[c] Model mutually adjusted for HIV serostatus, nutritional status, anemia, age, sex, research study, causative organism, and level of consciousness (n = 1,115).

[d] Includes only those children aged ≤120 months.

[e] Predicts failure perfectly; a multivariable model including all terms in the full model except for malnutrition found an OR of 0.05 with a 95%CI of (0.01, 0.39).

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Table 6

Univariate and multivariate logistic regression models of the association between HIV serostatus, anthropometrics, demographics, and causative organism and permanent sequelae in children with acute bacterial meningitis, Queen Elizabeth Central Hospital, Blantyre, Malawi, 1997--2010. OR = Odds ratio, CI = confidence interval; alive, no permanent sequelae is used as the reference group.

	Unadjusted Model [OR, (95%CI)][a]	Adjusted Model [OR, (95%CI)][b]
HIV Serostatus (*n* = 814)		
Negative	Ref	Ref
Positive	1.08 (0.80, 1.46)	0.88 (0.56, 1.38)
Nutritional Status(*n* = 865)[c]		
Normal	Ref	Ref
Underweight	0.76 (0.51, 1.13)	0.98 (0.56, 1.71)
Malnourished	0.86 (0.56, 1.32)	1.33 (0.71, 2.49)
Wasted	1.08 (0.66, 1.76)	1.71 (0.84, 3.50)
Severely Wasted	1.24 (0.65, 2.38)	1.00 (0.37, 2.68)
Anemia (Hb g/dL) (*n* = 795)		
No anemia (≥11.0)	Ref	Ref
Mild anemia (8.0--10.9)	**1.86 (1.26, 2.76)**	1.33 (0.72, 2.46)
Moderate/severe anemia (<8.0)	**2.82 (1.88, 4.24)**	1.60 (0.80, 3.21)
Age in Months (*n* = 976)		
<6	**2.29 (1.59, 3.31)**	1.74 (0.92, 3.31)
6-24	**1.66 (1.22, 2.28)**	1.35 (0.75, 2.44)
25-60	1.41 (0.95, 2.08)	1.22 (0.66, 2.23)
>60	Ref	Ref
Sex (*n* = 974)		
Female	Ref	Ref
Male	0.82 (0.64, 1.06)	0.92 (0.62, 1.35)
Causative Organism (*n* = 978)		
Streptococcus pneumoniae	**2.72 (1.84, 4.01)**	**1.84 (1.03, 3.29)**
Haemophilus influenzae type b	**1.65 (1.06, 2.56)**	1.57 (0.81, 3.03)
Neisseria meningitidis	**0.31 (0.15, 0.64)**	**0.36 (0.12, 1.05)**
Salmonella spp	**8.33 (3.96, 17.5)**	**3.02 (0.94, 9.64)**
Other/NOS	1.52 (0.77, 3.01)	1.42 (0.53, 3.81)
No Growth	Ref	Ref
Study (n = 1,762)		
Study 1	Ref	Ref
Study 2	**4.26 (3.20, 5.68)**	**5.40 (3.48, 8.38)**
Study 3	**1.99 (1.25, 3.15)**	**2.24 (1.18, 4.28)**
Level of Consciousness (*n* = 976)		
Normal	Ref	Ref
Impaired (BCS 3--4)	**2.70 (1.95, 3.75)**	**2.75 (1.72, 4.42)**
Coma (BCS ≤2)	**3.33 (2.45, 4.53)**	**3.27 (2.02, 5.29)**
Days of Fever (*n* = 934)	**1.09 (1.03, 1.16)**	1.02 (0.93, 1.13)
Plasmodium Infection (n = 969)		
Absent	Ref	
Present	0.70 (0.46, 1.06)	

[a] Model contains only the variable of interest.

[b] Model mutually adjusted for HIV serostatus, nutritional status, anemia, age, age, sex, causative organism, research study, and level of consciousness ($n = 56$).

[c] Includes only those children aged ≤120 months.

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