

Aetiology, outcomes, and in-hospital mortality predictors of suspected paediatric central nervous system infections in southwestern Uganda: a prospective cohort study



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Summary

Background Central nervous system (CNS) infections remain a major cause of paediatric morbidity and mortality in sub-Saharan Africa. We aimed to describe the aetiology and outcomes of paediatric CNS infections in southwestern Uganda and identify predictors of in-hospital mortality.

Methods Children aged 0–12 years with suspected CNS infections were recruited upon admission and followed until discharge, transfer, or death between January 2019 and September 2020 at two major hospitals in southwestern Uganda. Blood and cerebrospinal fluid (CSF) underwent routine diagnostics and BioFire FilmArray ME Panel testing. We used modified Poisson regression with robust variance to identify predictors of in-hospital mortality.

Findings Among the 212 children enrolled, in-hospital mortality was 15% (95% CI: 11–20%), while 18% (95% CI: 13–23%) were discharged with neurological sequelae. At admission, delayed capillary refill (adjusted risk ratio [aRR] = 5.9; 95% CI: 1.8–20), symptomatic anaemia (aRR = 2.7; 95% CI: 1.1–7.0), and elevated peripheral white blood cell count (aRR = 3.3; 95% CI: 1.8–6.1) were independently predictive of fatal outcomes. *Plasmodium* species were detected in 20% (n = 42) of cases, and HHV-6 in 9% (n = 19), including instances of co-infection. Among bacterial pathogens in CSF, *Streptococcus pneumoniae* (11/24) was the most frequently identified, followed by *Haemophilus influenzae* (4/24) and *Neisseria meningitidis* (4/24).

Interpretation Despite advances in infectious disease control, children with suspected CNS infections in southwestern Uganda continue to experience high mortality and neurological sequelae. Strengthened prevention, rapid diagnostics, and simple bedside markers such as delayed capillary refill, symptomatic anaemia, and elevated WBC count could enable earlier risk stratification and improved outcomes in low-resource settings.

Funding The Swedish Research Council (Vetenskapsrådet), European Commission Horizon Europe Research and Innovation Program, and the European Research Council.

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Keywords: Central nervous system infections; Meningitis; Aetiology; Paediatrics; Hospital mortality; Low-resource settings

Introduction

Central nervous system (CNS) infections remain a significant global public health challenge, with over two million cases annually and high mortality rates of up to

50%, and nearly 100% in untreated bacterial meningitis.^{1,2} Survivors often suffer long-term neurological sequelae, such as motor impairments, speech, vision, and

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Research in context

Evidence before this study

We conducted a comprehensive literature search in PubMed and Web of Science to identify studies on the aetiology, outcomes, and mortality predictors of paediatric central nervous system (CNS) infections, particularly in Uganda and the broader sub-Saharan Africa region. In PubMed, we used MeSH terms and synonyms related to children (e.g., “Child”, “Infant”), CNS infections (e.g., “Central Nervous System Infections”, “Meningitis”, “Encephalitis”), aetiology, outcomes, and mortality predictors, combined with geographic terms such as “Uganda” and “East Africa”. The same keywords were adapted for the search on Web of Science. Our search identified one relevant study on paediatric central nervous system infections in Uganda (2009–2012) and additional studies on cryptococcal and TB meningitis. No recent comprehensive studies addressed CNS infection aetiology or outcomes post-pneumococcal vaccine introduction, highlighting a critical evidence gap addressed by this study.

Added value of this study

This study provides a timely analysis of the impacts resulting from five years since the introduction of the pneumococcal vaccine, offering insights into how the epidemiology of pediatric CNS infections is being affected in a low-resource setting. It underscores the clinical significance of non-specific signs, such as symptomatic anemia and delayed capillary refill

in children suspected of CNS infections, emphasizing their value in early detection of infection severity. Additionally, the findings highlight the importance of addressing paediatric anaemia at the community level, pointing to a broader need for integrated child health strategies beyond infection control.

Implications of all the available evidence

Despite expanded vaccine programmes and ongoing malaria control efforts, evidence shows that both *Plasmodium* spp and *Streptococcus pneumoniae* remain major causes of severe neurological disease in children across sub-Saharan Africa. Our findings align with this broader evidence, indicating that pneumococcal conjugate vaccine introduction has not eliminated pneumococcal CNS disease and that malaria remains a significant additional burden. The accumulated evidence also underscores the value of non-specific but readily identifiable clinical features such as anaemia, impaired perfusion, and altered consciousness, for severity assessment in resource-limited settings. The available data indicate that effective reduction in CNS infection burden will require integrated approaches that combine infection prevention with strategies to identify and manage paediatric anaemia at community and facility levels. Further work is needed to monitor pathogen trends and refine early-risk stratification tools.

behavioural disorders.³ The burden of these infections is disproportionately high among children in low- and middle-income countries, where access to timely diagnosis and treatment is often limited.¹

CNS infections are caused by bacterial, viral, fungal, or parasitic pathogens, many of which are treatable if diagnosed early.⁴ Common bacterial pathogens include *S. pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*, while viral causes include enteroviruses and arboviruses.⁴ The prevalence of pathogens varies by geography, season, age, immune status, and vaccination coverage, underscoring the need for context-specific data to guide clinical and public health responses.⁵

In Africa, the “meningitis belt”, spanning West, East, and Central Africa, has historically been the epicentre of CNS infections.¹ Although epidemics in this region have declined, 80% of meningitis cases now occur sporadically, including in Uganda, which borders this region.⁶ This highlights the need for locally optimised intervention strategies aligned with the WHO’s roadmap to defeat meningitis by 2030.⁶

Timely and differential diagnosis is essential for effective treatment and surveillance, especially amid rising antimicrobial resistance.⁷ While cerebrospinal fluid (CSF) culture and real-time polymerase chain

reaction (PCR) are diagnostic gold standards,⁴ they are often unavailable or have lengthy turnaround times in most low-resource settings. Syndromic diagnostic panels, which are now widely available, offer faster turnaround times but are costly⁸ and may exclude some locally relevant pathogens, such as non-typhoidal *Salmonella* and *Staphylococcus aureus*.⁹

In such contexts, clinical signs, symptoms, and basic laboratory tests become critical for initial triaging and treatment decisions.¹⁰ Indicators such as altered mental state, photophobia, irritability, blood and CSF white cell count, CSF protein, CSF glucose, and lactate, help assess severity and guide antibiotic use, although their accuracy varies in different settings.¹¹ Therefore, local epidemiological evidence is vital to refine diagnostic and treatment protocols.

Among other interventions, Uganda introduced the pneumococcal conjugate vaccine (PCV-10) in 2014, achieving over 90% coverage.¹² Surveillance data suggest a decline in pneumococcal meningitis incidence among children under five in sentinel districts following PCV-10 introduction.¹³ This study hypothesised that the etiologic profile and clinical outcomes of paediatric CNS infections have shifted in the post-PCV era. It aimed to describe the aetiology and clinical

outcomes of paediatric CNS infections in southwestern Uganda and identify predictors of in-hospital mortality.

Methods

Study design and setting

This was a prospective observational cohort study of children aged 0–12 years who were suspected of CNS infections upon admission to two hospitals in Mbarara, Uganda. The study is part of the PI-POC clinical trial (registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03900091) (registration number NCT03900091)) conducted at Mbarara Regional Referral Hospital (MRRH) and Holy Innocents Children's Hospital (HICH) in Uganda, from January 2019 to September 2020.¹⁴ HICH is a 60-bed private nonprofit children's hospital in Mbarara, offering inpatient and outpatient services, a basic clinical laboratory, and counselling services. MRRH is a 400-bed hospital that admits about 5000 newborns and children annually, serving the urban, peri-urban, and rural parts of southwestern Uganda, as well as neighbouring countries. The hospital is a teaching hospital, situated next to the Mbarara University of Science and Technology (MUST) and the Epicentre Mbarara Research Laboratory. The Epicentre Mbarara Research Laboratory is a biosafety level 3 facility accredited by Qualogy Limited, an international, independent accreditation system, under Good Clinical Laboratory Practice.

Participant recruitment and management

Eligibility criteria

A child was considered for inclusion if they had a fever in the past 48 h and any of the following: reduced level of consciousness (Blantyre coma score <4 or <5 for preverbal children less than or older than 9 months respectively, and a Glasgow coma scale of <15 for verbal children); prostration; hypotonia; hypertonia; irritability; neck stiffness or bulging fontanel; focal neurological sign; seizure; and the Kernig or Brudzinski sign for children older than 18 months.

Study procedures and data collection

Post-recruitment, patients were managed according to standard clinical protocols, with the added benefit of the FilmArray Meningitis/Encephalitis Panel (FA-ME) included in the diagnostic testing panel for study participants. Lumbar punctures were performed for patients without contraindications. Venous blood was collected for haematology, biochemistry, malaria testing, and bacterial culture. Study participants were followed up until discharge, with de-identified clinical information documented in case report forms (CRFs). Laboratory results were recorded in DISA LIMS and printed for clinical use. Data from the CRFs and laboratory results were double-entered into REDCap by two independent data clerks to ensure quality. The two entries for each patient were compared, and where they

differed, troubleshooting was conducted to determine the correct entry. Data triangulation was also conducted after the clinical trial to validate the accuracy of the electronic records.

Study variables

The outcomes of hospitalisation were death during hospitalisation, cure, discharged without neurological sequelae, transferred or discharged with neurological sequelae, and discharged against medical advice. The primary outcome variable was in-hospital mortality.

The predictive factors were selected based on the literature,¹⁵ the feasibility of assessment upon presentation to the two hospitals, and the availability of sufficient data. These factors comprised demographic variables such as age and sex (biologically determined at birth), as well as key clinical signs at admission. Clinical indicators included the eligibility criteria listed above. Additional clinical observations considered were hospitalisation within the past month, prior antimicrobial use, diarrhoea, jaundice, vomiting, cold extremities, and oedematous malnutrition. Laboratory parameters with rapid turnaround time were also included: CSF and blood glucose, CSF protein, CSF and blood white blood cell (WBC) counts, and malaria test results. CSF findings were dichotomised for some analyses using clinically established thresholds supported by the literature to facilitate clinical interpretability.¹⁶ Thresholds prompting rapid empirical treatment for suspected bacterial meningitis were defined as a CSF leukocyte count ≥ 10 cells/ μL , a CSF glucose ≤ 40 mg/dL (or 2.2 mmol/L), and CSF protein ≥ 100 mg/dL (≥ 150 mg/dL for neonates).¹⁷ Age-specific reference ranges were applied to categorize peripheral white cell counts as low, normal, or high: 4.1–15.8 $\times 10^9$ cells/L for children younger than 1 year; 4.9–13.6 $\times 10^9$ cells/L for those aged 1–5 years; and 4.4–11.5 $\times 10^9$ cells/L for children aged 6–12 years.¹⁶

The severity of cases at admission was determined using a composite algorithm informed by the World Health Organization (WHO) criteria for cerebral malaria and acute meningitis.¹⁸ The cases were further classified into confirmed, probable, possible, and cases with no evidence of CNS infection based on pathogen detection results from CSF, blood culture, and malaria testing, along with CSF biomarkers and the associated clinical syndromes as described by Overturf (2005).¹⁷ All children in the study had a detailed clinical neurological assessment done by the study paediatrician at admission, every 12 h during hospitalisation, and at discharge. The attending paediatricians for the study had experience in assessing, documenting, and classifying neurological deficits in African children with acute CNS infections. The neurological exam included gross and fine motor domains, language and speech, behaviour, cranial nerves (including vision, hearing, and speech), sensation, coordination, and

deep tendon reflexes (Supplementary Table S1). Findings were documented in a predesigned, pretested template for neurological examination. During data analysis, neurological sequelae were classified using the framework described by Edmond et al. (2010), which groups post-meningitis sequelae into major (severe) and minor (mild) categories.¹⁹ Major sequelae consistent with Edmond's major global burden of disease domains consisted of hemiplegia, seizures, blindness, extrapyramidal rigidity, and hearing loss. Mild sequelae included cerebral ataxia, hypotonia, cranial nerve dysfunction, and neuropsychiatric disorders.

Diagnostic testing

All the laboratory tests were done at the Epicentre Mbarara Research Laboratory. CSF analyses included microscopy, cytology, Gram staining, microbiology culture, and biochemistry. An aliquot of CSF was analysed on the FilmArray device. The instrument utilises multiplex PCR technology to detect up to 14 common CNS pathogens from a single sample, with a turnaround time of just over an hour and minimal sample handling requirements. The following pathogens are included in the testing panel: *Escherichia coli* K1, *H. influenzae*, *Listeria monocytogenes*, *N. meningitidis*, *Streptococcus agalactiae*, *S. pneumoniae*, Cytomegalovirus (CMV), Enterovirus, Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2), Human herpesvirus 6 (HHV-6), Human parechovirus, Varicella zoster virus (VZV), and *Cryptococcus neoformans/gattii*. Blood was tested for malaria using the SD Bioline Malaria Ag Pf/Pan RDT (Standard Diagnostics), followed by malaria microscopy if the rapid diagnostic test (RDT) was positive, as a gold standard for *Plasmodium* species identification. Additionally, a complete blood count (Sysmex XN-550, Sysmex Corp. Kobe, Japan) and biochemistry (Roche Cobas C111 Roche, Basel, Switzerland) were performed.

Statistical analysis

All analyses were conducted using R (version 4.5.0) and Stata (version 15; StataCorp, College Station, TX, USA). Baseline demographic, clinical, and laboratory characteristics were summarised descriptively. Categorical variables were presented as frequencies and proportions. Continuous variables were categorised using clinically established paediatric reference ranges to enhance clinical interpretability and applicability in routine care. The primary outcome was in-hospital mortality. Mortality and neurological sequelae proportions were estimated with corresponding 95% confidence intervals (CIs). Comparisons between children who died and those who survived were performed using the χ^2 test, or Fisher's exact test when expected cell counts were fewer than five. Continuous variables were assessed using the Wilcoxon rank-sum tests.

This study was designed primarily as a descriptive epidemiological investigation; therefore, the sample size and number of deaths were determined by case accrual rather than by a priori power calculations. The objective of the exploratory analyses was therefore to examine the direction and magnitude of associations for clinically important predictors. A broader set of variables was included in the model because outcomes in suspected CNS infections arise from multiple inter-related clinical domains. As such, our analyses are best interpreted as hypothesis-generating rather than confirmatory.

Associations between independent variables and in-hospital mortality were initially assessed using univariable log-binomial regression, with results expressed as crude risk ratios (RRs) and 95% CIs. Because the log-binomial model failed to achieve convergence in multivariable analyses, modified Poisson regression with robust variance estimation was used to estimate adjusted risk ratios (aRRs) and corresponding 95% CIs.

The final multivariable model included variables associated with in-hospital mortality at $p < 0.05$ in univariable analyses, together with age, which was retained based on biological plausibility. Collinearity among covariates was assessed using variance inflation factors (VIFs), with values > 5 indicating problematic collinearity; highly correlated variables were excluded to improve model stability. Because this was a prospective cohort study with real-time data collection, missing data were minimal, and analyses were conducted using complete-case analysis. All statistical tests were two-sided, and a p -value < 0.05 was considered statistically significant.

Ethics approval

Ethical clearance was granted by the Institutional Ethical Review Board of Mbarara University of Science and Technology in Uganda (ref. 22/05-18) and the Regional Ethical Review Board in Stockholm, Sweden (ref. 2018/1676-31/1) in 2018, with the approval extended in 2022. Approval was also granted by the Uganda National Council for Science and Technology (UNCST Reference No HS 2508). The clinical trial and this sub-study were conducted in line with the Helsinki Declaration and following the guidelines for Good Clinical Practice and Good Laboratory Practice. Written informed consent was obtained from the parents or legal guardians of all participating children prior to enrolment, with emphasis on the provision of standard practice regardless of their decision to participate.

Role of the funding source

The funding sources for this study had no role in its design, the collection, analysis, and interpretation of data, the writing of this report, or the decision to submit the paper for publication.

Results

Two hundred and twelve paediatric patients suspected of CNS infections were recruited into the clinical trial: 89 were admitted to MRRH and 123 to HICH (Fig. 1). The patients' ages ranged from 0 to 155 months, with a median age of 10 months (IQR, 1–50 months). Since the cohort consisted mostly of neonates and infants (31%), participants were split into clinically meaningful age groups: neonates (0–28 days), infants (1–12 months), young children (1–5 years), and school-aged children (5–12 years). 78% (n = 165) of the patients were under 5 years old, and most of them were male (Table 1).

Out of the 212 patients, 194 had successful lumbar puncture (LP) while seven patients had contraindications, eight had unsuccessful LP, and parents refused the procedure in three cases. Fifty percent of the participants (n = 106) had received anti-infective medication in the 7 days prior to admission, from referring facilities or drug shops, including 24% (n = 50) who had taken antibiotics. The rest had received either unknown medication (n = 25), only antipyretic (n = 19), or

Characteristic	N = 212 ^a
Sex	
Male	131 (62%)
Female	81 (38%)
Age (months)	
	10 (1, 50)
Age group	
<1 month	66 (31%)
1–12 month	46 (22%)
1–5 years	53 (25%)
>5 years	47 (22%)
Length of hospitalisation (days)	
	8 (4, 13)

^an (%); Median (Q1, Q3).

Table 1: Demographics and outcomes of study participants.

antimalarial medication (n = 12). Most of the patients (n = 202, 95%) were categorised as severe according to the WHO malaria and meningitis guidelines (Supplementary Table S2). As a result, 94% (n = 200) received appropriate antimicrobials within one day of admission. Post-admission treatment consisted

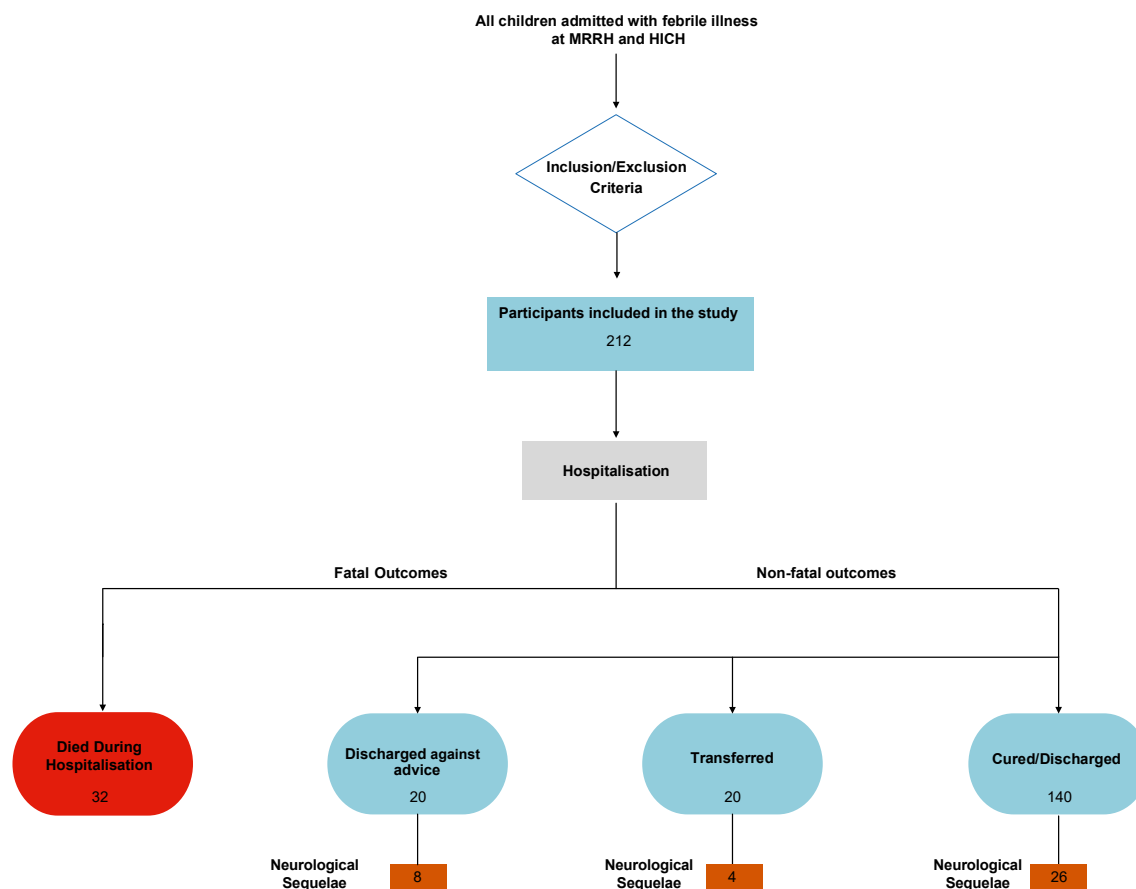


Fig. 1: Participant flow chart. Flow chart of study participants' recruitment and their outcomes of hospitalisation. MRRH, Mbarara Regional Referral Hospital; HICH, Holy Innocents Children's Hospital.

primarily of empiric antibiotic therapy for all patients, supplemented by antimalarials for patients who tested positive for *Plasmodium* spp. Ceftriaxone was the most frequently administered antibiotic ($n = 177$, 83%) (see [Supplementary Table S3](#)). The most common antibiotic combination was ceftriaxone plus benzylpenicillin ($n = 83$), aligning with WHO-recommended regimens for suspected bacterial meningitis. Ampicillin and gentamicin, the recommended first line for neonatal sepsis, were used in 38 admissions. Triple-agent combinations were less common ($n = 15$), consisting mostly of ampicillin plus gentamicin plus cloxacillin or ceftriaxone. Adjunctive therapy with dexamethasone was rarely given ($n = 4$). Acyclovir was administered primarily to patients who tested positive for viral pathogens on the FA-ME ($n = 18$).

Outcomes of hospitalisation

The median length of hospitalisation, which constituted the time patients were followed up, ranged from 0 to 50 days, with most patients discharged before 13 days of hospitalisation. 54% (95% CI: 47–60%) of patients were cured and discharged without neurological sequelae; 7% (95% CI: 5–12%) were transferred without neurological sequelae, and 6% (95% CI: 3–9%) self-discharged against medical advice, yet without neurological sequelae. Conversely, 33% of the patients included in this study experienced poor outcomes during hospitalisation, with 15% ($n = 32$; 95% CI: 11–20%) dying during hospitalisation, while 18% ($n = 38$; 95% CI: 13–23%) developed neurological sequelae before discharge or transfer ([Fig. 2a](#)). More than two-thirds of the neurological sequelae were considered major ($n = 27$) according to the global

burden of disease domains of Edmond et al. (2010) (see [Supplementary Table S4](#)). The neurological sequelae were predominantly seizures ([Fig. 2b](#)), developing in 20 (11%) cases during hospitalisation, and hypotonia in 13 (7%) cases. Although the remaining sequelae were observed in fewer cases individually, they cumulatively affected 18 (8%) of the children. Some of the cases ($n = 11$) developed more than one sequela.

Signs, symptoms at admission, and associated mortality

Of the signs that qualified patients for inclusion in the study, seizures were the most prevalent (84%), followed by a non-traumatic reduced level of consciousness (82%) and prostration (80%). Although the presence of these signs did not differ significantly between survivors and non-survivors ([Table 2](#)), patients with either a history of seizures or seizures at admission had a decreased unadjusted risk of in-hospital mortality (cRR 0.46; 95% CI: 0.23–0.9) compared with those without seizures. The difference was, however, not statistically significant after adjustment ([Table 2](#)).

Irritability, neck stiffness, and hypotonia (48%, 45%, and 35%, respectively) were also highly prevalent among the patients. Neck stiffness and bulging of the fontanelle were both significantly associated with mortality ($p = 0.028$ and $p = 0.025$, respectively); however, the risk was not statistically significant after adjusting for other covariates. Patients with hypertonia were also associated with increased risk of in-hospital mortality (cRR 1.9; 95% CI: 1.0–3.5), which was also not statistically significant after adjusting for other covariates ($p = 0.57$).

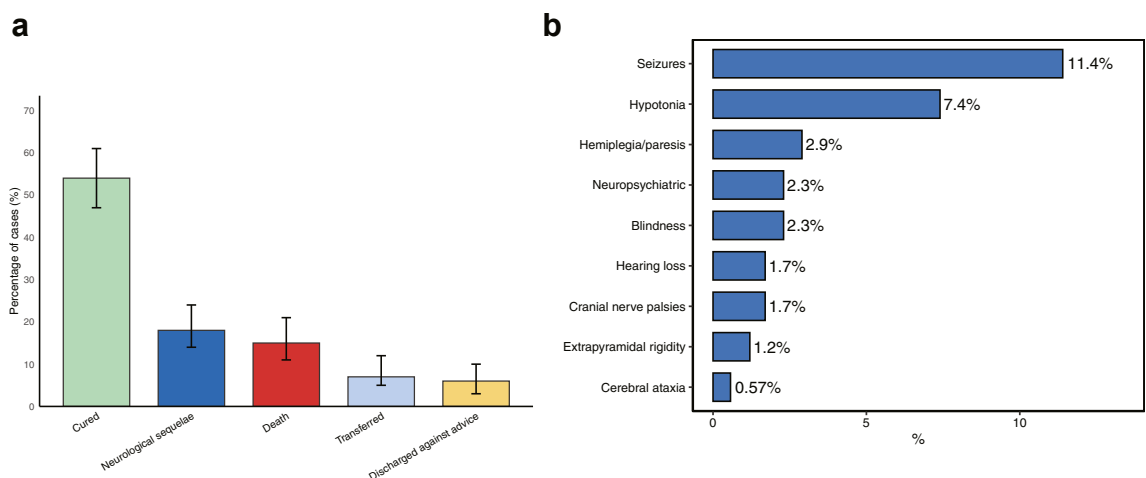


Fig. 2: a. Hospitalisation outcomes. The outcomes of hospitalisation ($N = 212$) include those who died, those who were discharged without neurological sequelae (Cured), those who were transferred without neurological sequelae, and individuals who self-discharged against medical advice without neurological sequelae. Error bars show 95% confidence intervals (CI). **b. Sequelae distribution in survivors.** Percentage distribution of neurological sequelae that developed among patients who survived hospitalisation ($N = 175$).

Characteristics	Overall N = 212	Died N = 32 ^a	Survived N = 180 ^a	p-value ^b	cRR (95% CI)	aRR (95% CI)	p-value
Demographics							
Sex, Female	81 (38%)	15 (47%)	66 (36%)	0.24	1.5 (0.8–2.8)		
Age group							
<1 month	66 (31%)	11 (34%)	55 (31%)	0.42	Ref	–	
1–12 month	46 (22%)	10 (31%)	36 (20%)		1.4 (0.62–3.0)	2.1 (0.47–9.2)	0.33
1–5 years	53 (25%)	5 (16%)	48 (27%)		0.6 (0.22–1.7)	0.57 (0.10–3.2)	0.53
>5 years	47 (22%)	6 (19%)	41 (23%)		0.9 (0.37–2.2)	0.33 (0.06–1.9)	0.22
Clinical signs of CNS infection at admission							
Hypotonia	39 (18%)	7 (22%)	32 (18%)	0.60	1.2 (0.57–2.6)		
Hypertonia	74 (35%)	16 (50%)	58 (32%)	0.052	1.9 (1.0–3.5)	1.2 (0.58–2.6)	0.58
Irritability	101 (48%)	13 (41%)	88 (49%)	0.63	0.7 (0.39–1.4)		
Neck stiffness	95 (45%)	21 (66%)	74 (41%)	0.028	2.1 (1.1–3.9)	2.3 (0.96–5.4)	0.06
Bulging fontanelle ^c	32 (15%)	9 (28%)	23 (13%)	0.025	2.2 (1.12–4.3)	–	
Focal neurological sign	8 (4%)	1 (3%)	7 (4%)	0.83	0.8 (0.13–5.2)		
Kernig sign	25 (12%)	2 (6%)	23 (13%)	0.60	0.5 (0.12–2.1)		
Brudzinski sign	18 (9%)	3 (9%)	15 (8%)	0.54	1.4 (0.42–4.3)		
Reduced consciousness ^c	173 (82%)	30 (94%)	143 (79%)	0.054	3.4 (0.84–14)		
Seizures ^c	179 (84%)	23 (72%)	156 (87%)	0.023	0.46 (0.23–0.9)	0.55 (0.25–1.2)	0.15
Prostration	168 (80%)	28 (87%)	140 (79%)	0.478	1.7 (0.62–4.5)		
General clinical characteristics at admission							
Jaundice	22 (11%)	3 (9%)	19 (11%)	0.20	1.5 (0.50–4.1)		
Vomiting	40 (19%)	7 (22%)	33 (19%)	0.66	1.2 (0.55–2.6)		
Diarrhoea	22 (11%)	7 (22%)	8 (15%)	0.02	3.4 (1.2–4.9)	1.5 (0.66–3.4)	0.34
Cold extremities	12 (5.7%)	5 (16%)	7 (4%)	0.02	3.1 (1.4–6.5)	–	
Symptomatic anaemia	18 (8.1%)	6 (19%)	12 (6%)	0.028	2.6 (1.3–5.5)	2.7 (1.1–7.0)	0.038
Delayed capillary refill	20 (9.8%)	11 (37%)	9 (5%)	<0.001	4.3 (2.4–7.9)	5.9 (1.8–20)	0.0030
Oedematous malnutrition	9 (4%)	5 (16%)	4 (2%)	0.001	4.1 (2.1–8.2)	0.8 (0.14–4.3)	0.76
CSF and blood tests							
Peripheral WBC count				0.01			
High	63 (34%)	16 (57%)	47 (29%)		2.9 (1.4–6.0)	3.3 (1.8–6.1)	<0.001
Low	11 (6%)	2 (7%)	9 (6%)		2.1 (0.52–8.2)	4.8 (1.1–21)	0.040
Normal	114 (61%)	10 (36%)	104 (65%)		Ref		
Elevated CSF protein (≥ 1 g/L)	79 (37%)	13 (41%)	66 (37%)	0.08	1.4 (0.62–3.1)	1.3 (0.58–3.1)	0.50
Elevated CSF WBC (≥ 10 cells/ μ l)	22 (11%)	4 (13%)	18 (12%)	0.75	1.1 (0.88–1.3)		
Low CSF glucose (≤ 2.2 mmol/L) ^c	21 (10%)	6 (29%)	15 (10%)	0.090	1.2 (0.94–1.5)	–	
Any pathogen detected	89 (42%)	12 (38%)	77 (43%)	0.97	1.02 (0.5–2.2)		
Bacterial	27 (13%)	5 (16%)	22 (12%)	0.57	1.04 (0.89–1.22)		
Viral	11 (5%)	2 (6%)	9 (5%)	0.67	1.01 (0.92–1.11)		
Parasitic	38 (18%)	3 (9%)	35 (19%)	0.89	0.78 (0.78–1.01)		
Mixed	13 (6%)	2 (6%)	11 (6%)	1.00	1.00 (0.91–1.10)		
No pathogen detected	123 (58%)	20 (62%)	103 (57%)	0.70	1.14 (0.71–1.84)		

cRR, crude risk ratio; aRR, adjusted risk ratio; CI, confidence interval; WBC, white blood cell; CSF, cerebrospinal fluid. Observations coded as not applicable were excluded from contingency analyses, as the exposure could not logically occur in those participants. CSF analyses were done for patients who had a successful lumbar puncture (N = 194). Significant associations (p < 0.05) are indicated by bold p values and risk ratios (95% confidence intervals). ^an (%). ^bPearson's Chi-squared test; Fisher's exact test. ^cEliminated from the model because of collinearity; Ref, Reference category.

Table 2: Clinical and laboratory characteristics of the patients and associated in-hospital mortality.

Among the non-specific clinical signs, having diarrhoea (cRR 3.4; 95% CI: 1.2–4.9), cold extremities (cRR 3.1; 95% CI: 1.4–6.5), symptomatic anaemia (cRR 2.6; 95% CI: 1.3–5.5), oedematous malnutrition (cRR 4.1; 95% CI: 2.1–8.2), and delayed capillary refill (cRR 4.3; 95% CI: 2.4–7.9) was associated with increased risk of fatal outcomes (Table 2). Patients with low or high blood WBC were associated with 4.8 and 3.3 times the risk of a fatal outcome, respectively.

After adjusting for relevant covariates and potential confounders (Table 2 and Fig. 3), delayed capillary refill was associated with an increased risk for in-hospital mortality (adjusted risk ratio (aRR) 5.9 (95% CI: 1.8–20.0)). Children presenting with symptomatic anaemia also had 2.7 times the risk of dying relative to those without anaemia (aRR 2.7; 95% CI: 1.1–7.0). A low or high peripheral WBC count was another predictor of a fatal outcome (aRR 4.8 (95% CI: 1.1–21.0); aRR 3.3

(95% CI: 1.8–6.1) respectively). A low peripheral WBC count, however, had a low prevalence, leading to a less precise estimate of its effect. Age and seizures were included in the model; however, their associations with the outcome were not statistically significant.

Aetiology of the suspected CNS infections

Of the 212 children in the trial, 42% (n = 89) had at least one pathogen identified by FilmArray, CSF culture, blood culture, or malaria RDT (Table 3). Malaria was predominantly caused by *P. falciparum* and other malaria species and was detected in 20% (n = 42) of the children suspected of CNS infections. All but four of these cases (90%, n = 38) fulfilled the criteria for cerebral malaria, being accompanied by a GCS ≤11 OR BCS ≤3 as well as seizures and general prostration. Bacterial pathogens were found in CSF in 11% (n = 24) of patients by FA-ME analyses, and in blood in 7% (n = 15) by blood culture. *S. pneumoniae* was the most common bacterial pathogen identified in CSF by the FA-ME and CSF culture (5%, n = 11), followed by *H. influenzae* (2%, n = 4) and *N. meningitidis* (2%, n = 4). An analysis of vaccination rates in the cohort showed that PCV-10 vaccination was more common among children without *S. pneumoniae* detection (57%, 113/199) than among those in whom the pneumococcal pathogen was detected (46%, 6/13) (see Supplementary Tables S5 and S6). HHV-6 was the second most prevalent pathogen detected in the cohort, with 19 patients found to have it in their CSF, as a single pathogen (n = 12) and as a co-pathogen with bacteria or malaria

(n = 7). All HHV-6 cases who died (n = 3) had bacterial co-infection. CMV and Enterovirus were the other two viral pathogens detected in the CSF from the cohort.

Pathogenic bacteria were isolated from blood cultures in 15 cases. Blood culture enabled the detection of *S. pneumoniae* in two additional cases: one in which CSF could not be obtained, and the other in which CSF culture showed no growth and was negative on the FA-ME. Co-infections were found in several cases, while some cases had the same pathogen detected on more than one platform. Other pathogens isolated only through blood culture, namely *Klebsiella pneumoniae*, *S. aureus*, *Enterococcus faecium*, *Enterococcus faecalis*, *Acinetobacter baumannii*, and coagulase-negative *Staphylococcus* spp, were not part of the FA-ME panel.

Overall, 49% of the children had either a confirmed (36%, n = 76), probable (6%, n = 12), or possible (7%, n = 15) central nervous system infection, as defined by Overturf (2010).¹⁷ Diagnosis for the remaining 51% was based on clinical syndromes compatible with central nervous system infections. CSF parameters varied across aetiological classes, with the largest differences observed in leukocyte count and protein concentrations (Supplementary Tables S7 and S8). Among patients with a bacterial pathogen detected in the CSF or in blood, 23% (n = 6) had normal CSF leukocyte count, glucose, and protein levels. The differences in CSF parameters among patients with neurological sequelae were not statistically significant between mild and severe cases (Supplementary Table S8).

Pathogen/Aetiology	CSF culture (n, % of 186)	FA-ME (n, % of 193)	Blood culture (n, % of 210)	Malaria test (n, % of 208)	Total detected (n, % of 212)
Bacterial					
<i>Streptococcus pneumoniae</i>	1 (0.5%)	11 (5.7%)	2 (1.0%)	–	13 (6.1%)
<i>Neisseria meningitidis</i>	1 (0.5%)	4 (2.1%)	0 (0.0%)	–	4 (1.9%)
<i>Haemophilus influenzae</i>	1 (0.5%)	4 (2.1%)	1 (0.5%)	–	4 (1.9%)
<i>Escherichia coli</i>	0 (0.0%)	2 (1.0%)	0 (0.0%)	–	2 (1.0%)
<i>Streptococcus agalactiae</i>	0 (0.0%)	3 (1.6%)	0 (0.0%)	–	3 (1.4%)
CoNS	0 (0.0%)	–	3 (1.4%)	–	3 (1.4%)
<i>Klebsiella pneumoniae</i>	0 (0.0%)	–	3 (1.4%)	–	3 (1.4%)
<i>Staphylococcus aureus</i>	0 (0.0%)	–	2 (1.0%)	–	2 (1.0%)
<i>Enterococcus faecium</i>	0 (0.0%)	–	2 (1.0%)	–	2 (1.0%)
<i>Enterococcus faecalis</i>	0 (0.0%)	–	1 (0.5%)	–	1 (0.5%)
<i>Acinetobacter baumannii</i>	0 (0.0%)	–	1 (0.5%)	–	1 (0.5%)
Viral					
HHV-6	–	19 (9.0%)	–	–	19 (9.0%)
Enterovirus	–	2 (1.0%)	–	–	2 (1.0%)
Cytomegalovirus	–	2 (1.0%)	–	–	2 (1.0%)
Parasitic					
Malaria	–	–	–	42 (19.8%)	42 (19.8%)
Any pathogen detected	–	–	–	–	89 (42%)
No pathogen detected	–	–	–	–	123 (58%)

FA-ME, FilmArray Meningitis/Encephalitis panel; RDT, rapid diagnostic test; N, number of patients tested by the diagnostic platform; CoNS, coagulase-negative *Staphylococcus*.

Table 3: Pathogens detected by diagnostic modality.

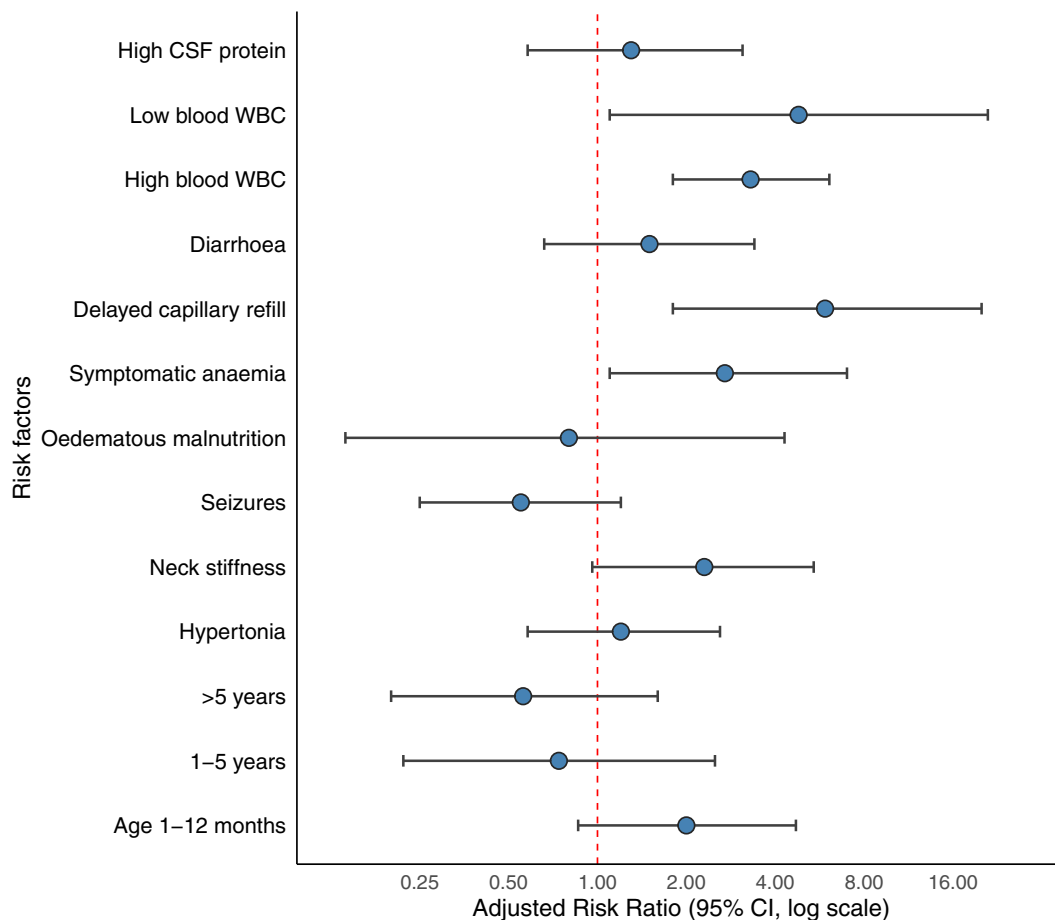


Fig. 3: Adjusted risk ratios and 95% CIs for in-hospital mortality using a modified Poisson regression model. Seizures, delayed capillary refill, and symptomatic anaemia were the primary covariates in the model, with adjustment for age. See [Table 2](#) for details.

Discussion

This study provides a detailed assessment of hospitalisation outcomes, prognostic indicators, and the aetiologies of suspected paediatric CNS infections. The observed rates of mortality and neurological sequelae reflected the continuing severity of these infections in a low-resource setting, despite improvements in diagnostic and clinical care over the past decades. Amid sustained vaccination efforts and improved malaria diagnostics and treatment in Uganda, our analysis found that *Plasmodium* spp and *S. pneumoniae* remain the most common pathogens. Notably, no pathogen was identified in more than half of the cases; however, the aetiological spectrum identified shows the complexity and often multifactorial nature of CNS infections, highlighting a significant diagnostic need. By examining both clinical presentation and underlying aetiologies, two admission signs, capillary refill and symptomatic anaemia, and elevated peripheral WBC count emerged as significant predictors of fatal outcomes.

The predominance of male children in this cohort is consistent with broader regional epidemiological patterns in sub-Saharan Africa, where higher male admission rates have been observed for acute illnesses.²⁰ Although our data do not clarify the underlying mechanisms, biological differences in immune responses may partly explain the greater susceptibility to infections among male children compared to females.²¹

In this study, in-hospital mortality was 15%, and an additional 18% of the cases left the hospitals with disabling neurological sequelae. The in-hospital mortality observed aligns with previous reports from similar low-resource settings, where mortality rates for paediatric CNS infections typically range from 15% to 25%.⁹ Notably, a study conducted at the same site a decade earlier reported a comparable mortality rate of 18%, indicating a likely yet minor impact from public health interventions.⁹ This stagnation calls for increased investment in both clinical management and preventive strategies for CNS infections in this resource-limited

setting. The neurological sequelae observed in 21% (n = 38) of the survivors were slightly higher than previous findings in the same context, where these long-term sequelae were reported in 13.5% of survivors.⁹ These persisting impairments highlight substantial burden exerted by CNS infections in low-resource settings and the need for structured post-discharge follow-up and rehabilitation interventions. The effect of adjunctive corticosteroids, particularly dexamethasone, was not assessed in this cohort because their use was minimal, consistent with current evidence indicating limited benefit in paediatric populations in low-income settings and contraindications in neonates.²²

Delayed capillary refill was the strongest independent predictor of in-hospital mortality in this cohort, reinforcing existing evidence that this simple bedside assessment for cardiovascular compromise is a critical marker of poor prognosis in acutely ill children.²³ Consistent with our findings, a previous study demonstrated that a predictive model incorporating age, capillary refill time, respiratory rate, and altered mental status had high accuracy in identifying children at risk of death.²⁴ Relatedly, symptomatic anaemia also emerged as a significant and potentially modifiable risk factor for mortality. In Uganda, childhood anaemia remains highly prevalent, driven by endemic malaria and other nutritional and infectious causes.²⁵ The wide confidence intervals pointed to the limited number of fatal events and the low prevalence of certain exposures. These findings, however, underscore the importance of routine screening and timely management of anaemia - not only as a comorbidity, but also as a target for mortality prevention in children presenting with severe infections involving the CNS.

The identified predictors - delayed capillary refill, symptomatic anaemia, and abnormal peripheral white blood cell counts - are not specific to CNS infections but likely reflect systemic disease severity, including impaired perfusion and inflammatory responses. The lack of association between neurological features or CSF parameters and mortality supports the interpretation that outcomes were driven primarily by overall physiological compromise rather than CNS-specific pathology.

The aetiology of CNS infections in children in Uganda remains a complex interplay between malaria, bacteria, and viruses. Although identified as the most common pathogen, malaria was not associated with an increased risk of death in this study, likely due to awareness, availability of prompt and accessible diagnostic testing, and treatment.²⁶ Malaria is, however, still a serious threat in Uganda and warrants continued community sensitisation campaigns for prompt care-seeking, along with integrated community case management strategies.²⁶ *S. pneumoniae* was the most common bacterial pathogen detected in this paediatric

cohort, despite the introduction of PCV-10 vaccine locally in 2014 and the high vaccination rates in the country and region.¹² The detection rate for *S. pneumoniae* was, however, slightly less than the 8% observed in the earlier study.⁹ Serotype replacement could be the most plausible explanation for the minimal to static reduction in detection rates; however, this could not be ascertained, as pneumococcal serotyping was not done on the isolates in this study, and external surveillance evidence of *S. pneumoniae* serotypes is lacking in this context. With clear serotype distribution and trends, recommendations for upgrading to PCV-13 could be more conclusive.

Several pathogens were identified only by blood culture and were not detected in CSF. *K. pneumoniae* was one of these pathogens identified in three neonates, although it is usually isolated from adults and immunocompromised patients.²⁷ This pathogen has, however, been reported as a cause of sepsis in children across several African countries.²⁸ It is therefore likely that most of the pathogens detected through blood culture were sepsis cases. Non-typhoidal *Salmonella* was not isolated from this cohort, despite being found in 2.4% (n = 11) of cases in a previous study in this setting.⁹ This finding confirms the conclusion about the fluctuating pattern of the burden of invasive non-typhoidal *Salmonella* in sub-Saharan African countries.²⁹

The presence of the FilmArray device in the study enabled molecular detection of HHV-6, CMV, and Enterovirus in 11% of the cases, in addition to malaria and bacterial pathogens. The range of viral pathogens, however, was limited to those on the FA-ME panel, compared with other studies in Uganda and other African countries, where a wider range of viruses was detected in CNS infections.^{9,30} The clinical significance of detecting HHV-6 remains unclear due to its potential latency and chromosomal integration.³¹ Serological tests for IgM positivity or quantitative PCR in blood and CSF were unavailable to confirm active infection. However, the findings by Mallewa et al. in Malawi cement the burden and significance of viral aetiology in paediatric CNS infections in Africa.³⁰ The study found the viral detection frequency comparable to that reported in Europe, the Americas, and Asia; however, notable differences were observed in the spectrum of pathogens and the presence of co-infections, which were associated with increased risk of mortality. This underscores the imperative for investment in appropriate diagnostic tools to detect viral aetiologies and determine the true burden of viral infections.

The strength of this study was the prospective collection of data on a broad range of indicators and risk factors, which enabled consistency. The main limitation was the lack of post-discharge follow-up, with sequelae observed only during hospitalisation. Some of the

patients might have fully recovered or developed delayed neurological complications after discharge. Additionally, the time-lapse from symptom onset to appropriate treatment was not captured and thus was not assessed as a risk factor. Data on ethnicity were not collected for reporting, although the Mbarara population includes all ethnic groups in Uganda and small proportions of people of Asian or European origin. Data from the previous study in the same setting were also unavailable for an in-depth comparison of pathogen incidence and associated clinical characteristics. Future research could therefore explore other prehospital contributing factors for unfavourable outcomes; develop and validate scalable, low-cost molecular diagnostics for early pathogen detection to complement routine microbiology; and extend the follow-up period for neurological sequelae to assess neurodevelopmental trajectories and modifiable risks.

Overall, there are still many gaps in quantifying the burden of CNS infections in Uganda and other sub-Saharan African countries using standardised approaches that can inform diagnostics, treatment, and prevention strategies. This study highlights persistently high mortality and disabling sequelae among children with suspected CNS infections. The predominance of malaria and *S. pneumoniae* underscores the need for improved diagnostic tools, timely and targeted treatment strategies, and broader-valency pneumococcal vaccines. Importantly, the independent prognostic value of delayed capillary refill, symptomatic anaemia, and elevated WBC count in blood suggests that general indicators of cardiovascular collapse may be more predictive of outcomes than CNS-specific signs alone. These findings call for a more holistic clinical assessment approach and support the integration of broader clinical indicators into triage and management protocols.

Contributors

Phuthumani Mlotshwa: conceptualisation, data curation, formal analysis, methodology, visualisation, writing—original draft, writing—review & editing. Elias Kumbakumba: conceptualisation, data curation, funding acquisition, methodology, validation, project administration, resources, writing—review & editing. Dan Nyehangane: data curation, investigation, methodology, project administration, writing—review & editing. Reza Rasti: conceptualisation, methodology, project administration, writing—review & editing. Richard Migisha: formal analysis, visualisation, writing—review & editing. Milly Nassejje: investigation, validation, writing—review & editing. Deborah Nanjebe: data curation, investigation, writing—review & editing. Yap Boum II: investigation, methodology, resources, writing—review & editing. Juliet Mwangi-Amumaire: conceptualisation, funding acquisition, methodology, resources, writing—review & editing. Tobias Alfvén: conceptualisation, methodology, funding acquisition, resources, supervision, writing—review & editing. Giulia Gaudenzi: conceptualisation, data curation, methodology, formal analysis, validation, visualisation, funding acquisition, project administration, resources, supervision, writing—review & editing. PM, RM, and GG verified the data and had access to the raw data. GG had the final responsibility for the decision to submit for publication.

Data sharing statement

De-identified individual participant data, the data dictionary, and statistical code used in this study can be made available by request to the corresponding author by email. For some requests, access may require submission of a protocol, approval by the principal investigators, and the signing of a data access agreement.

Declaration of interests

All the authors declare no competing interests.

Acknowledgements

We would like to acknowledge and thank the participants and staff at MRRH and HICH, as well as the staff at Epicentre Mbarara Research Laboratory, for their support in carrying out the trial, sample analysis, data cleaning, and triangulation. This study has been made possible through the funding from the following bodies: The Swedish Research Council (Vetenskapsrådet, grant 2015-03217, 2019-05170, 2020-05396), European Commission Horizon Europe Research and Innovation Program (Grant Agreement N° 101057596), and the European Research Council (Consolidator grant 615458).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanafr.2026.100050>.

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