Mortality after hospital discharge among children younger than 5 years admitted with suspected sepsis in Uganda: a prospective, multisite, observational cohort study

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Summary

Background Substantial mortality occurs after hospital discharge in children younger than 5 years with suspected sepsis, especially in low-income countries. A better understanding of its epidemiology is needed for effective interventions to reduce child mortality in these countries. We evaluated risk factors for death after discharge in children admitted to hospital for suspected sepsis in Uganda, and assessed how these differed by age, time of death, and location of death.

Methods In this prospective, multisite, observational cohort study, we recruited and consecutively enrolled children aged 0–60 months admitted with suspected sepsis from the community to the paediatric wards of six Ugandan hospitals. Suspected sepsis was defined as the need for admission due to a suspected or proven infectious illness. At admission, trained study nurses systematically collected data on clinical variables, sociodemographic variables, and baseline characteristics with encrypted study tablets. Participants were followed up for 6 months after discharge by field officers who contacted caregivers at 2 months and 4 months after discharge by telephone and at 6 months after discharge in person to measure vital status, health-care seeking after discharge, and readmission details. We assessed 6-month mortality after hospital discharge among those discharged alive, with verbal autopsies conducted for children who had died after hospital discharge.

Findings Between July 13, 2017, and March 30, 2020, 16 991 children were screened for eligibility. 6545 children (2927 [44·72%] female children and 3618 [55·28%] male children) were enrolled and 6191 were discharged from hospital alive. 6073 children (2687 [44·2%] female children and 3386 [55·8%] male children) completed follow-up. 366 children died in the 6-month period after discharge (weighted mortality rate 5·5%). Median time from discharge to death was 28 days (IQR 9–74). For the 360 children for whom location of death was documented, deaths occurred at home (162 [45·0%]), in transit to care (66 [18·3%]), or in hospital (132 [36·7%]) during a subsequent readmission. Death after hospital discharge was strongly associated with weight-for-age Z scores less than –3 (adjusted risk ratio [aRR] 4·7, 95% CI 3·7–5·8 *vs* a Z score of >–2), discharge or referral to a higher level of care (7·3, 5·6–9·5), and unplanned discharge (3·2, 2·5–4·0). Hazard ratios (HRs) for severe anaemia (<7g/dL) increased with time since discharge, from 1·7 (95% CI 0·9–3·0) for death occurring in the first time tertile to 5·2 (3·1–8·5) in the third time tertile. HRs for some discharge vulnerabilities decreased significantly with increasing time since discharge, including unplanned discharge (from 4.5 [2·9–6·9] in the first tertile to 2·0 [1·3–3·2] in the third tertile) and poor feeding status (from 7·7 [5·4–11·0] to 1·84 [1·0–3·3]). Age interacted with several variables, including reduced weight-for-age Z score, severe anaemia, and reduced admission temperature.

Interpretation Paediatric mortality following hospital discharge after suspected sepsis is common, with diminishing, although persistent, risk during the first 6 months after discharge. Efforts to improve outcomes after hospital discharge are crucial to achieving Sustainable Development Goal 3.2 (ending preventable childhood deaths under age 5 years).

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Introduction

Although substantial improvements in child mortality have been achieved during the past three decades,[1] mortality after hospital discharge has emerged as a key priority to further improve child survival, especially in low-income countries. Successful transition between facility and community care is a crucial component of comprehensive care for acute illness and should not be decoupled from hospital care, as is often the case.[2] A more granular understanding of events occurring

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Research in context

Evidence before this study

We conducted a systematic literature search of MEDLINE, Embase, and CINAHL, from database inception to May 27, 2022, for studies conducted in low-income or low-middle-income countries that enrolled more than 100 children who had been admitted to hospital, had at least 8 days of follow-up after discharge, and that obtained vital status at the end of follow-up (appendix pp 17–21). 46 eligible studies were identified and used to calculate pooled mortality 6 months after hospital discharge. Children enrolled in studies of malnutrition had the highest pooled rates of mortality 6 months after hospital discharge (pooled mortality 10·3%, 95% CI 6·0–15·5), followed by studies of anaemia (6·3%, 3·4–9·9), studies of diarrhoeal illness (4·2%, 2·7–6·1), studies enrolling all hospital admissions (4·2%, 3·1–5·3), studies of pneumonia (3·5%, 0·9–7·6), and studies of malaria (3·2%, 1·9–4·7; appendix pp 22–24). Of the studies that provided proportions of deaths after discharge versus deaths in hospital, studies of children with anaemia had the highest proportion of deaths after discharge (71%), whereas studies of children with pneumonia (28%) and malaria (42%) had the lowest proportions. Among risk factors that were measured and eligible for pooling, unplanned discharges (hazard ratio [HR] 4·60, 95% CI 2·41–8·79), severe malnutrition (3·61, 2·66–4·91), being HIV positive (3·56, 3·01–4·20), and previous admissions to hospital (2·75, 1·43–5·29) were associated with the highest overall pooled HRs for mortality after hospital discharge.

Added value of this study

To our knowledge, this multisite observational cohort study is the largest prospective study to date to evaluate mortality after hospital discharge in a low-income country. Our findings are largely in line with previous work, substantiating key populations of risk, important risk factors for mortality after hospital discharge, and the approximate proportion of overall deaths that occur after hospital discharge. The large number of outcomes in this study facilitated novel analyses that have not been possible previously, including an assessment of how age and the timing of mortality after discharge act as effect modifiers for various risk factors. We found that age interacts with many risk factors, but particularly with nutritional status (with the association with risk of mortality decreasing with increasing age) and anaemia (with the association with risk of mortality increasing with increasing age). We also reported the varying associations between risk factors and risk of mortality during the first 14 days, days 15–58, and days 59–183 following discharge. HRs for mortality increased up to four times between the first and last of these observation periods after discharge for those with sociodemographic vulnerabilities or severe anaemia. Discharge vulnerabilities, such as unplanned discharges or poor feeding, showed diminishing HRs over time, decreasing as much as six times between the first and last observation periods.

Implications of all the available evidence

To date, care after hospital discharge has not received sufficient attention in policy or clinical practice. The results of this study, along with previous findings, help to establish a robust evidence base that can be used to inform the development of programmes that facilitate an evidence-based, child-centred approach to ensuring safe transitions between hospital-based and community-based care. Combined with risk-stratification criteria, which are currently under development, interventions can be developed that ensure that optimal follow-up continues during key periods of increased risk of mortality after discharge on the basis of individual characteristics of the child.

during the period after hospital discharge is urgently required to guide interventions and policy decisions regarding resource allocation.[3]

See Online for appendix

Robust epidemiological data for paediatric mortality after hospital discharge in low-income countries are scarce, although several studies have been published in the past 5 years.[2,4–7] Mortality after discharge results from the complex convergence of a series of causal factors, outlined in the 2022 Childhood Acute Illness and Nutrition (CHAIN) Network study.[5] This prospective cohort study of 3101 children aged 2–23 months with acute illness admitted to hospital in diverse sites across sub-Saharan Africa and south Asia established that almost half of mortality occurs following hospital discharge. These findings suggest that mortality after discharge involves a heterogeneous set of circumstances and that efforts to improve survival after discharge should entail interventions across several domains.

Our systematic review found that consistently reported features of children at increased risk of mortality after discharge include malnutrition, illness severity (at admission and discharge), and socioeconomic factors (eg, poverty or maternal education; appendix pp 17–24).[2,8] However, substantial epidemiological gaps remain, including how age interacts with known risk factors. Furthermore, although several studies have reported high levels of at-home deaths,[2] risk factors for these deaths are poorly understood. Moreover, although many deaths occur early during the period after hospital discharge, how factors at admission affect the timing of deaths after discharge is unclear. These data are imperative in establishing prediction models and interventional programmes that address the complexities of paediatric mortality after hospital discharge.

The Global Burden of Diseases reported that in 2017, an estimated 2·9 million deaths of children under 5 years of age were due to sepsis, the majority of which occurred in low-income and-middle income countries.[9] In the same year, the World Health Assembly and WHO unanimously adopted a resolution to improve, prevent, diagnose, and manage sepsis.[10] Although most studies

that have examined mortality after hospital admission have included high proportions of children admitted because of infectious diseases, sepsis has not previously been the focus of these studies.[2]

This study aimed to improve understanding of the heterogeneous nature of mortality after hospital discharge by examining risk factors by age, location of death, and time of death among children younger than 5 years admitted to hospital with suspected sepsis in Uganda. This is necessary if the Sustainable Development Goal 3.2 of ending preventable deaths of newborns and children under 5 years of age is to be met.[11,12]

Methods

Study design

This prospective, multisite, observational cohort study analysed outcomes after discharge of a combined dataset comprising two prospective observational cohorts of children with suspected sepsis aged 0 months to less than 6 months and aged 6 months to 60 months at the time of admission to hospitals in Uganda. The study enrolled participants aged 0 months to less than 6 months and 6 months to 60 months from four hospitals in Uganda: Mbarara Regional Referral Hospital (Mbarara, southwest Uganda), Holy Innocents Children's Hospital (Mbarara, southwest Uganda), Masaka Regional Referral Hospital (Masaka, central Uganda), and Jinja Regional Referral Hospital (Jinja City, east Uganda). Children aged 0 months to less than 6 months were also enrolled from Villa Maria Hospital (Masaka, central Uganda) and Uganda Martyrs Hospital (Ibanda, southwest Uganda). In total, these public and faith-based facilities have a catchment area that includes 30 districts with a total population of approximately 8·2 million individuals, including approximately 1·4 million children younger than 5 years during the study period.[13] Participants were followed up until 6 months after discharge.

This study was approved by the Mbarara University of Science and Technology Research Ethics Committee (15/10–16), the Uganda National Institute of Science and Technology (HS 2207), and the University of British Columbia–Children and Women's Health Centre of British Columbia Research Ethics Board (H16–02679). This Article adheres to the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[14] The study protocol is available online.

Participants

In both cohorts, we consecutively enrolled children who required admission to hospital and had a confirmed or suspected infection (both of which were measured by the treating medical team). We have previously shown that approximately 90% of children admitted to hospital with a proven or suspected infection in Uganda meet the International Pediatric Sepsis Consensus Conference (IPSCC) definition for sepsis,[15] which defines sepsis as the presence of systemic inflammatory response syndrome combined with a confirmed or suspected infection.[16] Children who resided outside the hospital catchment area or who were admitted for a short-term observation period (<24 h), trauma, or immediately after birth (ie, without first being discharged home) were excluded. Written informed consent was obtained from the parent or legal guardian of all study participants.

Procedures

All data collection tools are available through the Smart Discharges study dataverse.[17] All data were collected at the point of care with encrypted study tablets and these data were then uploaded to a Research Electronic Data Capture[18,19] database hosted at the BC Children's Hospital Research Institute (Vancouver, BC, Canada). Studies of both cohorts were conducted by the same investigative team who used the same research staff to enrol and follow up all participants. Enrolment of each cohort was independently funded, but the protocols were the same for both cohorts, including the frequency and duration of follow-up.

At admission, trained study nurses systematically collected data on clinical variables, sociodemographic variables, and baseline characteristics. Clinical data included anthropometry (to establish malnutrition status), vital signs, simple laboratory variables (eg, glucose, malaria rapid diagnostic test [RDT], HIV RDT, haematocrit, and lactate), clinical signs and symptoms, comorbidities, and health-care history, including previous hospital admissions. Sociodemographic variables and baseline characteristics included maternal and household details such as maternal age, education, and HIV status; distance of home from facility; household size; use of bed-nets; and the availability of clean drinking water. Information on sex was extracted from medical records. At discharge, study nurses also obtained discharge status (ie, routine discharge, referral to higher level of care, or unplanned discharge) and feeding status (subjectively defined as feeding well or feeding poorly). The discharge diagnosis was abstracted from the medical record. Field officers contacted caregivers at 2 months and 4 months after discharge by telephone and at 6 months after discharge in person to measure vital status, any occurrence of health-care seeking after discharge, and readmission details. Verbal autopsies were conducted for children who had died after hospital discharge (appendix p 9).

For the **study protocol**, see https://doi.org/10.5683/SP3/QRUMNQ

Statistical analysis

The primary goal of the cohort study was to develop separate post-discharge mortality prediction models for both age cohorts. For the cohort aged 0 months to less than 6 months, we established that a target sample size of 2700 children would be sufficient, assuming an expected outcome rate of 7·5%; for the 6 month to 60 month cohort, we calculated a sample size of 3500 assuming an outcome rate of 5·0%. These models will be reported in a subsequent publication. Furthermore,

on the basis of these sample sizes and assumed outcome rates, we are able to estimate the mortality rates to within 1·0% in the cohort aged 0 months to less than 6 months and to within 0·7% in the cohort aged 6–60 months.

Data from both cohorts were combined and analysed as a single dataset. We used periods of overlapping enrolment (72% of total enrolment months) between the two cohorts to establish site-specific proportions of children aged 0 to <6 months and 6 to 60 months (appendix p 10). These proportions were used to weight the cohorts to estimate overall mortality. We assessed 6-month mortality after hospital discharge among those discharged alive.

Descriptive data were used to describe the population, including medians with IQRs for continuous variables and counts with percentages for categorical variables. Age-stratified Kaplan-Meier survival curves were used to estimate the cumulative hazard for overall mortality and mortality after discharge according to four predefined age strata (ie, 0 to <2 months, 2 to 6 months, >6 to 24 months, and >24 to 60 months). For Kaplan-Meier curves, follow-up began at discharge and ended at last follow-up date (censored), date of death, or 6 months after hospital discharge.

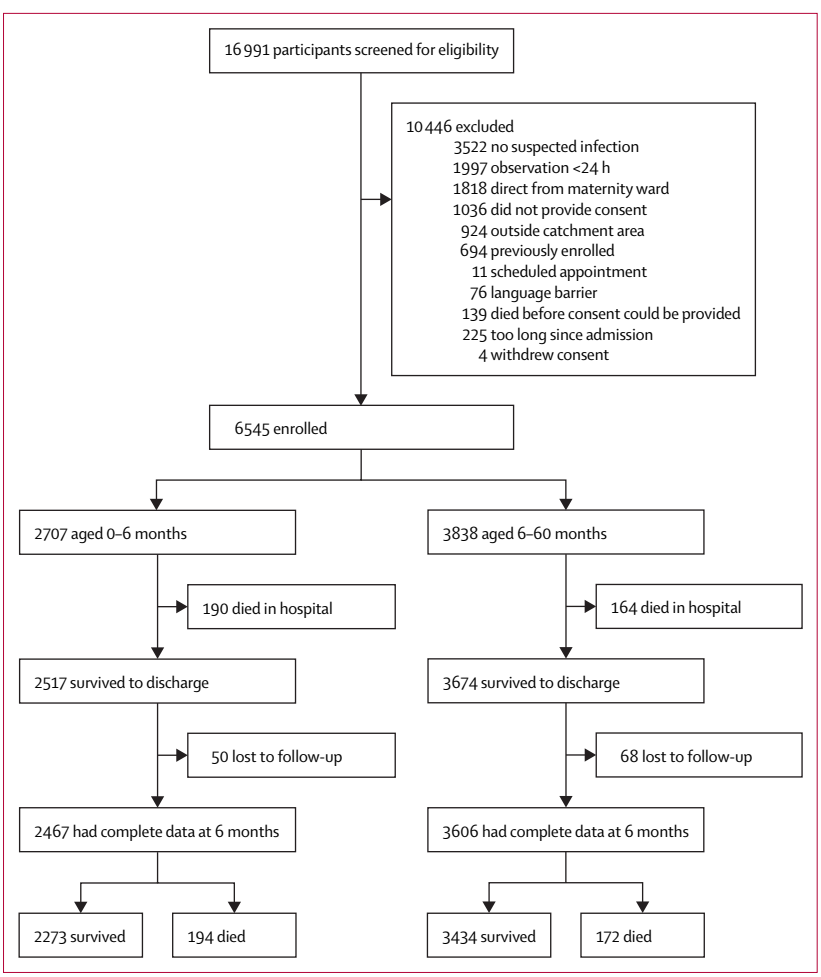


Figure 1: **Study profile**

To assess clinical and sociodemographic factors associated with mortality 6 months after hospital discharge, we used Poisson models with robust standard errors to estimate risk ratios (RRs) adjusted for age, sex, and site of enrolment.[20] We opted to treat the mortality outcome as binary as a low proportion (2%) of children did not complete 6-month follow-up. Site of enrolment was included as a fixed effect (as opposed to a random effect) because of the low number of sites included.[21] For all continuous predictors, we analysed the relationship in two ways, with a linear term and using regression splines to allow for possible non-linearity (specifically, with regression cubic polynomial splines, via B-spline bases, with knots at the boundaries, 25th, 50th, and 75th percentiles). Furthermore, when different thresholds are used clinically for a continuous variable (eg, mid-upper-arm circumference [MUAC]), we also categorised the variable and analysed these thresholds.

Based on findings from our analyses, we further described the participants who died by assessing possible interactions with age and potential time-dependency in the association between risk factors and mortality after discharge. Because of the number of factors, we opted to restrict these analyses to those with $p<0·01$ for the estimated RR, recognising that this approach might exclude other factors that could interact with age or vary over time. Possible multiplicative interactions were assessed with logistic regression models, including an interaction between a regression spline for age and the other factor of interest. Results have been displayed graphically as marginal effects plots with corresponding 95% CIs.[22] To assess the possible time-dependency of risk factors, we divided the 6-month period after hospital discharge into tertiles, dividing deaths after discharge evenly between these tertiles and fitting Cox models to each. For each of these models, participants were followed up to the earliest of three dates (ie, death, loss to follow-up, or end of the tertile). A heatmap was produced to visualise the magnitude of change in hazard ratios (HRs) across the three periods with the HR from the first period as the reference.

To assess the possible association of predictors on location of death, a multinomial logistic regression was fitted with location of death as the categorical outcome variable. The categories were: dying in hospital at readmission (the reference category), dying at home, or dying in transit to seeking care. Results were summarised as odds ratios, with corresponding 95% CIs and p values. Statistical significance was defined as $p<0·05$. These models were restricted only to those who died after discharge. We compared our results to the existing literature by conducting a random effects meta-analysis to pool proportions of those who died by available risk factors using generalised linear mixed effect models.

Missing values were low and imputed with k-nearest neighbours in all analyses. The primary aim of all analyses was to describe characteristics of participants who died, and not to assess causal effects or possible interventions to reduce mortality after hospital discharge. We did not adjust for multiple comparisons. Analyses were conducted in Stata/MP version 15.0, R version 4.1.3, and RStudio version 2022.2.3 (RStudio, Boston, MA, USA).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report, or in the decision to submit for publication.

Results

Participants were recruited to the cohort of children aged 6–60 months between July 13, 2017, and July 2, 2019, and to the cohort aged 0 months to less than 6 months between Jan 11, 2018, and March 30, 2020. Enrolment in these cohorts ended when the desired sample size was reached. 16 991 consecutively admitted children aged 0–60 months were screened. After exclusion of 10 446 children who did not meet study inclusion criteria, 6545 were enrolled; 2707 were enrolled into the 0–6-month cohort and 3838 were enrolled into the 6–60-month cohort (figure 1). 603 (9·9%) of 6073 participants had missing haemoglobin data and 200 (3·3%) of 6073 participants had missing feeding-at-discharge data; all other variables had minimal or no missing data (appendix p 26). Baseline characteristics are provided in the table.

Overall, the weighted 6-month mortality rate (in hospital and after discharge) was 10·9%. The overall median duration between hospital admission and death was 9 days (IQR 2–45). The mean follow-up time was 175 days, and the maximum was 183 days.

6191 children were discharged from hospital alive, of whom 118 (1·9%) were lost to follow-up at 6 months. Of the 6073 children for whom we have data, 194 (7·9%) of 2467 died after hospital discharge in the cohort aged 0–6 months and 172 (4·8%) of 3606 died after hospital discharge in the cohort aged 6–60 months, corresponding to a weighted 6-month mortality after discharge of 5·5%. Of 720 deaths, 366 occurred after hospital discharge, constituting 50·8% of total mortality. Of 361 verbal autopsies completed for deaths after discharge, the most common specific diagnoses assigned were pneumonia (96 [26·6%]), malaria (31 [8·6%]), diarrhoea (29 [8·0%]), and meningitis (27 [7·5%]; appendix p 9). Suspected sepsis deaths were also common (81 [22·4%]) and represented cases in which a generalised infection was suspected.

Malnutrition was commonly identified at admission and was associated with increased risk of mortality after hospital discharge (table). All anthropometric measures were also associated with increased risk of mortality after hospital discharge; for example, a weight-for-age Z score less than –3 had an adjusted RR (aRR) of 4·7 (95% CI

	n (%) or median (IQR)	aRR (95% CI)
Baseline characteristics		
Sex		
Male	3386 (55·8%)	1·0 (0·8 to 1·2)
Female	2687 (44·2%)	1·03 (0·84 to 1·26)
Age, years	0·8 (0·2 to 1·6)	0·9 (0·8 to 1·0)
Hospital of admission		
Mbarara Regional Referral Hospital	1034 (17·0%)	..
Holy Innocents Children's Hospital	1259 (20·7%)	..
Masaka Regional Referral Hospital	1327 (21·9%)	..
Jinja Regional Referral Hospital	2018 (33·2%)	..
Villa Maria Hospital	121 (2·0%)	..
Uganda Martyrs Hospital	314 (5·2%)	..
Admission anthropometry		
MUAC, mm*	130 (115 to 144)	1·0 (1·0 to 1·0)
<110 or <115	1195 (19·7%)	5·2 (3·9 to 7·0)
110–120 or 115–125	1110 (18·3%)	2·3 (1·6 to 3·1)
>120 or >125	3768 (62·1%)	0 (ref)
Weight-for-age Z score	–1·0 (–2·1 to –0·0)	0·7 (0·7 to 0·8)
<–3	818 (13·5%)	4·7 (3·7 to 5·8)
–3 to –2	836 (13·8%)	2·3 (1·7 to 3·0)
>–2	4419 (72·8%)	0 (ref)
Length-for-age Z score	–0·7 (–2·0 to 0·4)	0·8 (0·7 to 0·8)
<–3	729 (12·0%)	3·6 (2·9 to 4·5)
–3 to –2	784 (12·9%)	2·0 (1·5 to 2·7)
>–2	4560 (75·1%)	0 (ref)
BMI Z score	–0·9 (–2·2 to 0·3)	0·8 (0·8 to 0·9)
<–3	933 (15·4%)	3·0 (2·4 to 3·8)
–3 to –2	790 (13·01%)	2·02 (1·53 to 2·67)
>–2	4350 (71·6%)	0 (ref)
Weight-for-length Z score	–0·9 (–2·3 to 0·3)	0·9 (0·8 to 0·9)
<–3	949 (15·6%)	2·2 (1·8 to 2·8)
–3 to –2	771 (12·7%)	1·6 (1·2 to 2·1)
>–2	4353 (71·7%)	0 (ref)
Admission clinical assessment variables		
Time since last admission		
None	4078 (67·2%)	0 (ref)
<1 month	679 (11·2%)	2·0 (1·5 to 2·6)
1 month to 1 year	1042 (17·2%)	1·3 (1·0 to 1·7)
>1 year	274 (4·5%)	0·4 (0·2 to 1·0)
Care sought for current illness before admission	4025 (66·3%)	1·8 (1·4 to 2·2)
Parent-reported previous poor health		
Good health before this illness	5266 (86·7%)	0 (ref)
<1 week before this illness	164 (2·7%)	1·6 (0·9 to 2·6)
1 week to 1 month before this illness	349 (5·8%)	2·4 (1·8 to 3·3)
1 month to 1 year before this illness	294 (4·8%)	3·8 (2·9 to 5·1)

(Table continues in next column)

	n (%) or median (IQR)	aRR (95% CI)
(Continued from previous column)		
Referral	1852 (30·5%)	2·0 (1·7 to 2·5)
Previous antibiotic use	2673 (44·0%)	1·3 (1·1 to 1·6)
Previous antimalarial use	1402 (23·1%)	1·2 (1·0 to 1·6)
SpO_2	97 (93 to 99)	1·0 (1·0 to 1·0)
<90%	929 (15·3%)	1·7 (1·4 to 2·2)
90–95%	1423 (23·4%)	1·0 (0·8 to 1·3)
>95%	3721 (61·3%)	0 (ref)
Heart rate	146 (132 to 161)	1·0 (1·0 to 1·0)
Respiratory rate	49 (38 to 61)	1·0 (1·0 to 1·0)
Systolic blood pressure	93 (83 to 102)	1·0 (1·0 to 1·0)
Diastolic blood pressure	51 (43 to 60)	1·0 (1·0 to 1·0)
Axillary temperature, °C		
<36·5	734 (12·1%)	1·0 (0·7 to 1·4)
36·5–37·5	2906 (47·9%)	0 (ref)
37·6–39	1931 (31·8%)	0·9 (0·7 to 1·1)
>39	502 (8·3%)	0·4 (0·2 to 0·7)
Respiratory distress	1079 (17·8%)	1·4 (1·1 to 1·8)
Capillary refill ≥3 s	732 (12·1%)	1·4 (1·1 to 1·9)
Atypical BCS score	505 (8·3%)	2·0 (1·5 to 2·7)
Symptoms during the illness		
None	0	0 (ref)
Rash	634 (10·4%)	0·7 (0·5 to 1·0)
Cough <14 days	3615 (59·5%)	1·0 (0·8 to 1·2)
Cough ≥14 days	452 (7·4%)	1·3 (0·9 to 1·8)
Diarrhoea <14 days	1835 (30·2%)	0·9 (0·7 to 1·1)
Diarrhoea ≥14 days	150 (2·5%)	1·7 (1·0 to 2·9)
Fever <7 days	4968 (81·8%)	0·8 (0·6 to 1·0)
Fever ≥7 days	371 (6·1%)	1·2 (0·8 to 1·8)
Vomiting everything	1029 (16·9%)	1·1 (0·9 to 1·5)
Atypically tired	1215 (20·0%)	1·1 (0·9 to 1·5)
Swelling of both feet	298 (4·9%)	2·0 (1·4 to 2·9)
Changes in urine colour	696 (11·5%)	1·6 (1·2 to 2·1)
Producing less urine than usual	379 (6·2%)	1·6 (1·2 to 2·2)
Blood in faeces	107 (1·8%)	2·1 (1·3 to 3·5)
Seizure	854 (14·1%)	1·1 (0·8 to 1·4)
Coma	41 (0·7%)	2·1 (0·9 to 4·8)
Positive malaria test	1303 (21·5%)	0·7 (0·6 to 1·0)
RDT positive for HIV	173 (2·9%)	1·9 (1·3 to 3·0)
Haemoglobin status	12 (10 to 13)	0·9 (0·9 to 1·0)
Not anaemic: ≥11 g/dL	3961 (65·2%)	0 (ref)
Mild anaemia: 7–10 g/dL	1606 (26·4%)	1·3 (1·0 to 1·7)
Severe anaemia: <7 g/dL	506 (8·3%)	2·7 (2·1 to 3·6)
Lactate, mmol/L	2·1 (1·4 to 3·1)	1·1 (1·0 to 1·1) per mmol/L
Glucose, mmol/L		
<2·5	150 (2·5%)	1·8 (1·1–2·9)
2·5–8·3	5235 (86·2%)	0 (ref)
>8·3	688 (11·3%)	1·1 (0·8–1·5)

(Table continues in next column)

	n (%) or median (IQR)	aRR (95% CI)
(Continued from previous column)		
Maternal and sociodemographic characteristics		
Travel time to hospital		
<30 min	1299 (21·4%)	0 (ref)
30 min to <1 h	2138 (35·2%)	1·6 (1·1 to 2·3)
1 h to <2 h	1580 (26·0%)	2·8 (2·0 to 4·0)
2 h to < 3 h	720 (11·9%)	2·7 (1·8 to 4·1)
≥3 h	336 (5·5%)	3·7 (2·3 to 5·8)
Distance to facility, km	15·0 (4·6 to 32·1)	1·0 (1·0 to 1·0) per km
Maternal age, years	26 (23 to 30)	1·0 (1·0 to 1·0) per year
Household size	5 (3 to 6)	1·0 (1·0 to 1·1) per additional household member
Maternal education	2 (2 to 3)	0·7 (0·6 to 0·8)
No school or ≤P3	615 (10·1%)	0 (ref)
P4 to P7	2524 (41·6%)	0·7 (0·6 to 1·0)
S1 to S6	2088 (34·4%)	0·6 (0·4 to 0·8)
>S6	788 (13·0%)	0·3 (0·2 to 0·5)
Maternal HIV status		
Negative	5280 (86·9%)	0 (ref)
Positive	476 (7·8%)	1·5 (1·1 to 2·0)
Unknown	317 (5·2%)	1·6 (1·0 to 2·3)
Bed-net use		
Never	579 (9·5%)	1·2 (0·9 to 1·7)
Sometimes	466 (7·7%)	1·1 (0·8 to 1·6)
Always	5028 (82·8%)	0 (ref)
Boil, disinfect, or filter water	4409 (72·6%)	0·7 (0·6 to 0·9)
Discharge characteristics		
Length of stay, days	4 (3 to 6)	1·0 (1·0 to 1·0) per day
Discharge status		
Routine discharge	5122 (84·3%)	0 (ref)
Referred to higher level of care	189 (3·1%)	7·3 (5·6 to 9·5)
Unplanned discharge	762 (12·6%)	3·2 (2·5 to 4·0)
Feeding at discharge†		
Feeding well	5607 (92·3%)	0 (ref)
Feeding poorly	466 (7·7%)	4·0 (3·2 to 5·0)
Discharge diagnosis		
Malaria	1297 (21·4%)	0·7 (0·5 to 0·9)
Pneumonia	1893 (31·2%)	1·3 (1·1 to 1·6)
Bronchiolitis	306 (5·0%)	0·7 (0·4 to 1·2)
Upper respiratory tract infection	499 (8·2%)	0·5 (0·3 to 0·8)
Reactive airway disease or asthma	35 (0·6%)	0·6 (0·1 to 4·0)
Gastroenteritis or diarrhoea	940 (15·5%)	0·7 (0·5 to 0·9)
HIV-related or AIDS-related disease	53 (0·9%)	3·0 (1·7 to 5·3)
Meningitis or encephalitis	210 (3·5%)	2·1 (1·5 to 3·1)

(Table continues in next column)

	n (%) or median (IQR)	aRR (95% CI)
(Continued from previous column)		
Malnutrition	410 (6·8%)	3·0 (2·3 to 3·8)
Tuberculosis	81 (1·3%)	3·9 (2·5 to 6·0)
Skin or soft-tissue infection	187 (3·1%)	0·8 (0·5 to 1·6)
Measles	413 (6·8%)	0·4 (0·2 to 0·7)
Sepsis	1733 (28·5%)	0·9 (0·7 to 1·2)
Genetic or congenital disease	114 (1·9%)	4·9 (3·5 to 6·7)
Sickle cell anaemia	61 (1·0%)	0·9 (0·3 to 2·8)
Febrile seizure	24 (0·4%)	..
Other infection	131 (2·2%)	1·6 (0·9 to 2·8)
Other non-infection	234 (3·9%)	3·9 (2·9 to 5·1)

Data are n (%), median (IQR), or aRR (95% CI). All aRRs were adjusted for age, sex, and site of enrolment. aRR=adjusted risk ratio. BCS=Blantyre Coma Scale. MUAC=middle-upper-arm circumference. P=primary school, where the following number represents school years. RDT=rapid diagnostic test. S=secondary school, where the following number represents school years. SpO_2=oxygen saturation. *MUAC thresholds are given in mm for the 0 month to <6 month cohort and for the 6–60-month cohort. †Subjectively defined by study nurse.

Table: **Clinical risk factors for mortality 6 months after hospital discharge (n=6073)**

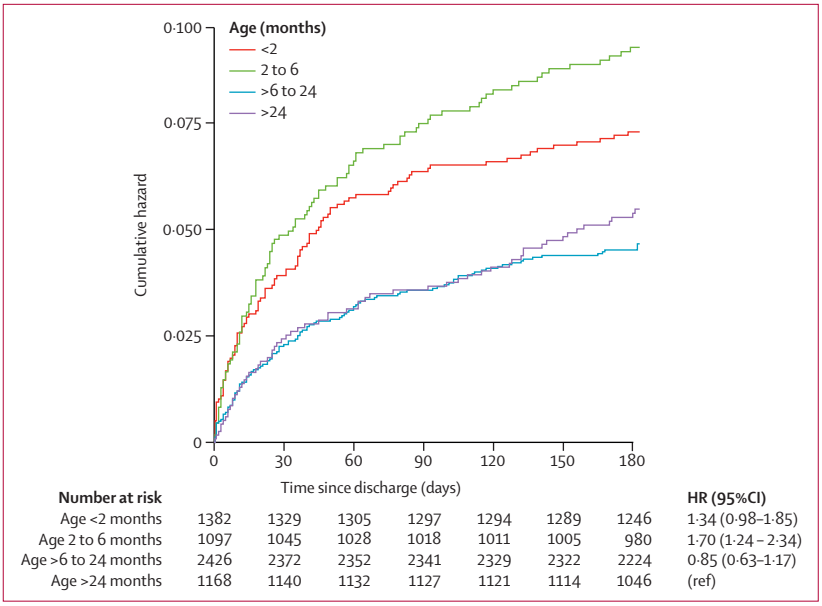


Figure 2: **Hazard curves for mortality after hospital discharge by age**
p value estimated from log-rank test.

3·7–5·8), with 818 (13·5%) of 6073 participants in this stratum. Most clinical signs and symptoms indicating more severe illness at admission conferred increased risk of mortality after discharge, although increased axillary temperatures at admission were associated with a reduced risk (table). Children with an RDT positive for HIV were also at increased risk of mortality after discharge (1·9, 1·3–3·0), whereas children with an RDT positive for malaria had a reduced risk (0·7, 0·6–1·0). Other factors associated with increased risk of mortality after discharge included severe anaemia (2·7, 2·1–3·6), elevated lactate (1·1 per 1 mmol/L increase, 1·0–1·1), and hypoglycaemia (1·8, 1·1–2·9). Several factors reflecting maternal and sociodemographic vulnerabilities were also associated with increased risk of mortality after discharge, including lower levels of maternal education, increased distance from hospital (both travel time and actual distance), maternal HIV, and not using boiled, disinfected, or filtered water (table).

Regarding factors related to hospital discharge, participants with an increased risk of mortality after discharge included those discharged with referral to another hospital for a higher level of care (7·3, 5·6–9·5), those with an unplanned discharge (3·2, 2·5–4·0), and those with poor feeding at discharge (4·0, 3·2–5·0). Discharge diagnoses associated with increased risk of mortality after discharge included pneumonia, HIV-related illnesses, tuberculosis, malnutrition, CNS infections, and genetic or congenital diseases. Diagnoses associated with a reduced risk of mortality after discharge included upper respiratory tract infections, malaria, acute gastroenteritis, and measles (table).

Among variables collected only in the cohort aged 0–6-months, all measured indicators of acuity were associated with an increased risk of mortality after hospital discharge, including atypical tone, pallor, and poor sucking when breastfeeding (appendix p 11). All measures of anthropometry (ie, MUAC, weight-for-age Z score, length-for-age Z score, BMI Z score, and weight-for-length Z score), oxygen saturation, and haemoglobin status showed non-linearity in their relationship with mortality (appendix p 25).

Among the four pre-defined age strata, younger age generally conferred a higher risk of mortality after discharge, although participants aged 2–6 months had the highest overall rate of mortality after discharge (figure 2). Several clinical variables showed differing associations with mortality depending on age (figure 3; appendix pp 2–7). Children presenting with axillary temperatures less than 36·5°C had an increasing probability of mortality after discharge with increasing age. However, other vital signs showed no interactive effect with age, including heart rate, respiratory rate, oxygen saturation, and systolic and diastolic blood pressure. Children with severe anaemia appeared to have a consistent risk of mortality across all age strata, whereas probability of death declined with increasing age among those with moderate or no anaemia. The effect of severely reduced weight-for-age and BMI-for-age Z scores appeared to diminish with increasing age (appendix p 2), although other anthropometric measures did not show clear interactions with age. Poor feeding at discharge and unplanned discharge also were associated with a greater risk of mortality in younger children than in older children (appendix p 7).

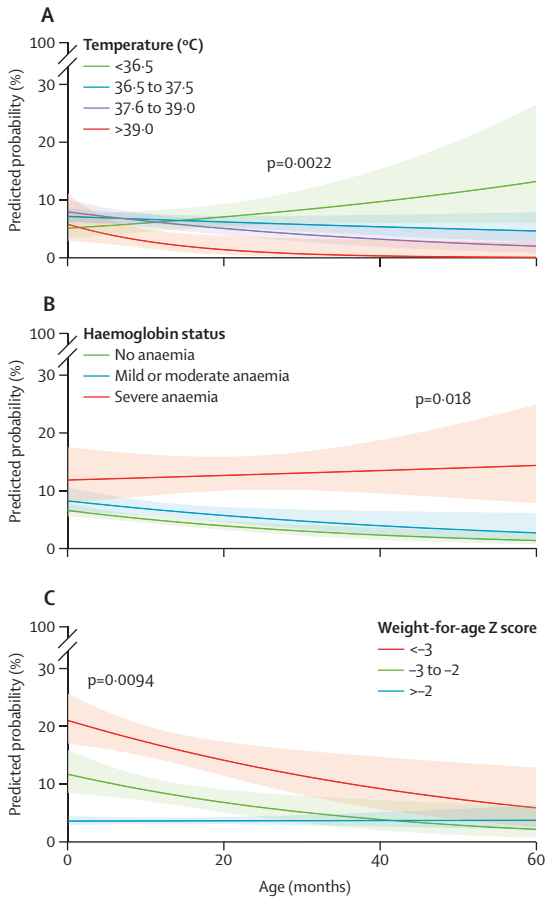


Figure 3: **Interactions between age and risk factors at hospital admission and their associations with risk of mortality after discharge**
(A) Interaction between age and temperature at hospital admission. (B) Interaction between age and haemoglobin status at hospital admission. (C) Interaction between age and weight-for-age Z score at hospital admission. Indicated p values are for the test of multiplicative interaction between age and the corresponding risk factor and are estimated by the likelihood ratio test comparing models with and without the interaction term. Shaded areas represent 95% CIs.

Median time from hospital discharge to death was 28 days (IQR 9–74). When time since discharge was separated into tertiles by deaths after discharge, we observed significant variation among several risk factors (figure 4; appendix p 12). Anthropometric measures showed persistent risk during the entire period, with peak HRs for several measures during the middle tertile. For severe anaemia, risk of mortality increased with time from discharge, with HRs increasing from 1·7 (95% CI 0·9–3·0) to 5·2 (3·1–8·5) between the first and third tertiles (p=0·00077). HRs for some discharge vulnerabilities decreased significantly with increasing time since discharge, including unplanned discharge (from 4·5 [95% CI 2·9–6·9] in the first tertile to 2·0 [1·3–3·2] in the third tertile [p<0·0001]) and poor feeding status (from 7·7 [5·4–11·0] to 1·84 [1·0–3·3; p<0·0001]). Similarly, for children who were referred to a higher level of care, the HR reduced from HR 17·7 (11·4–27·4) in the first tertile to 3·1 (1·3–7·1) in the third tertile (p<0·0001; appendix p 12). Social vulnerability, defined by little maternal education and further distance between home and admitting facility (both in terms of travel time and actual distance), showed increasing HRs with time after discharge. Mortality after hospital discharge most often occurred at home (n=162 [45·0%] of 360 children for whom data were available) or in hospital during a readmission (n=132 [36·7%] of 360), although nearly a fifth occurred in transit while seeking care (n=66 [18·3%] of 360. Neither travel time nor distance from home to the admitting hospital were associated with at-home or in-transit deaths. A discharge diagnosis of malnutrition was associated with at-home deaths, with an odds ratio of 1·9 (95% CI 1·0–3·6) compared with in-hospital deaths during a readmission (appendix p 13). Degree of malnutrition was only moderately associated with location of death, with lower age-adjusted MUAC, weight-for-length, and BMI-for-age Z scores associated with at-home (but not in-transit) deaths compared with in-hospital deaths during a readmission.

Discussion

In this prospective, multisite, observational cohort study of children younger than 5 years admitted to hospital in Uganda with suspected sepsis, we found that mortality after discharge was frequent, generally occurred in the first several weeks after discharge, was more common among younger children, and more often occurred in the community than during a readmission to hospital. Risk factors for mortality after discharge, including malnutrition, were largely in line with those reported in previous studies.[4,5,23] As such, strategies to improve care during the hospital-to-home transition should become urgent priorities in research, health policy, and practice.

In these two cohorts, more than half of all deaths after hospital discharge occurred during the first month after discharge. The associations between specific risk factors and the timing of mortality was notable, especially the increasing risk over time among children with severe anaemia and the decreasing risk over time among children with poor feeding at discharge and with unplanned discharges. A child-centred and resource-efficient approach to care should therefore ensure that interventions, and their timing, are linked to periods with the greatest risk of mortality. Early mortality could be partly addressed with a discharge readiness checklist, which has been effective in other settings.[24] A 2022 meta-analysis of mortality after discharge in malaria-endemic areas found that malarial anaemia conferred a lower risk of mortality after discharge risk than non-malarial anaemia,[6] which was also reflected in our study. A randomised controlled trial published in 2020 found that management of malarial anaemia after hospital discharge with malaria chemoprophylaxis reduced readmission and mortality after discharge[25] and WHO have included recommendations for

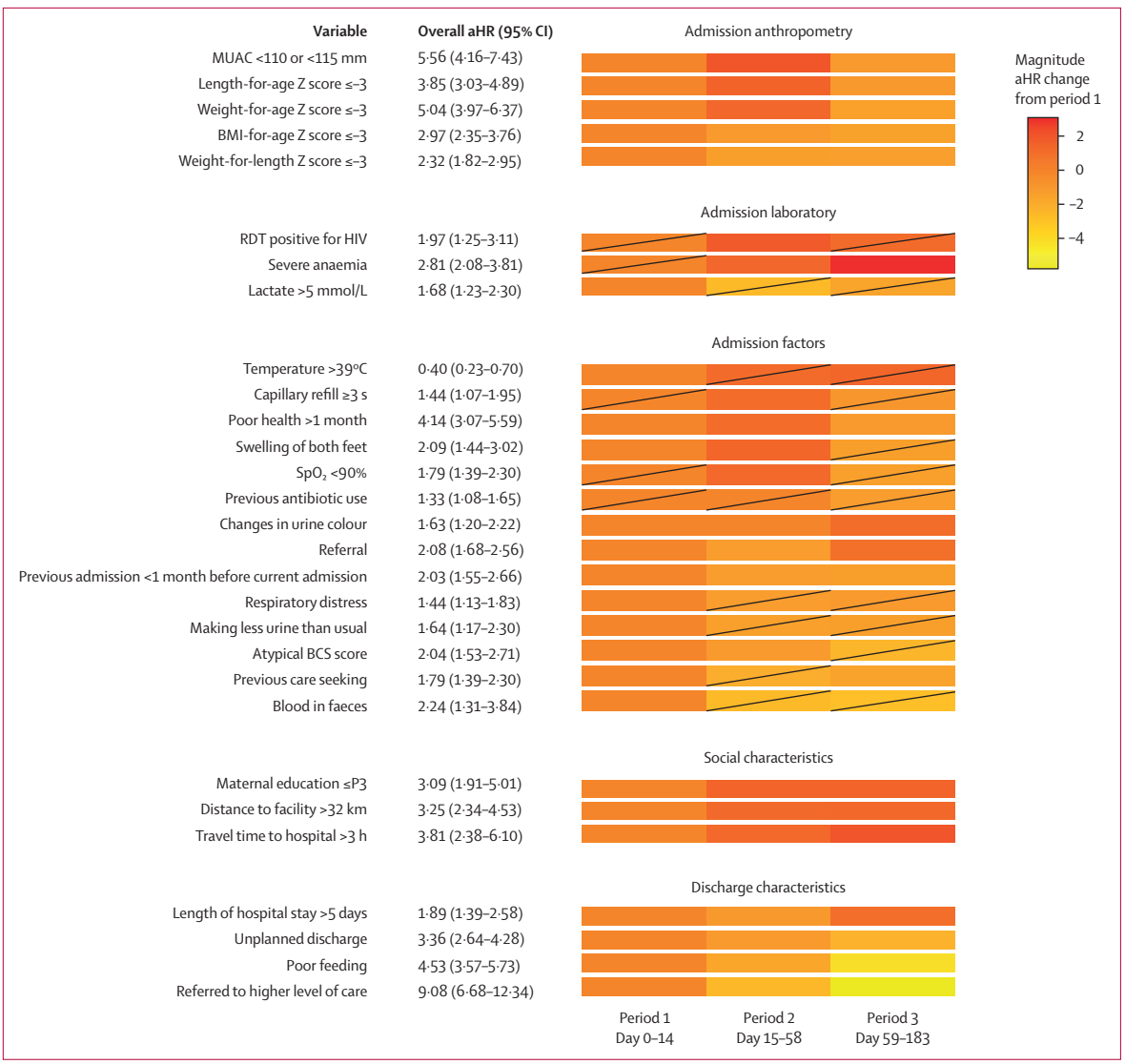


Figure 4: **Change in aHR over time**
The 6-month period after hospital discharge was divided into tertiles according to when deaths occurred and tertile-specific aHRs were calculated. The colours of the second and third periods show the magnitude change from the first period. Boxes containing diagonal lines represent aHRs that are not statistically significant, meaning that no significant association is observed between that particular risk factor and post-discharge mortality in that time period. For MUAC, the threshold of <110 mm applies to the cohort aged 0–6 months and <115 mm applies to the cohort aged 6–60 months. Feeding status was prospectively assessed at discharge by the study nurse and subjectively defined as either feeding well or feeding poorly. Actual aHR estimates are reported in the appendix (p 12). aHR=adjusted hazard ratio. BCS=Blantyre Coma Scale. MUAC=middle-upper-arm circumference. P=primary school. RDT=rapid diagnostic test. SpO_2=oxygen saturation.

malaria chemoprevention in children in their guidelines.[26,27] However, antibacterial chemoprophylaxis (co-trimoxazole), iron, or folate supplementation do not appear to improve outcomes after hospital discharge among children admitted with severe anaemia.[28]

Nearly half of the deaths that we observed occurred after the first month after discharge. Persistent vulnerability during the period after hospital admission is well described and is the subject of substantial and increasing interest. Although late deaths are not likely to be related to exacerbations of the index infection, several factors have been posited to be related to such deaths. Immune dysfunction among people who have recovered from sepsis, risks related to persistent vulnerability in the home and social environments, and new or existing comorbidities are all thought to be related to vulnerability to recurrent illness and death after discharge.[5,29,30] A better understanding of these and other potentially causal factors could help to accelerate the development of strategies to improve outcomes after hospital discharge.[12]

Although younger children had higher rates of mortality after discharge than older children, the group at highest risk were those aged 2–6 months. This could be because neonates admitted to hospital directly after

birth were excluded. The differences in clinical risk factors by age was notable, especially for anaemia, axillary temperature, and anthropometry. We found that the association between anaemia and risk of mortality after discharge was greatest in older children. The contribution of anaemia to mortality after discharge in older children has been described in a prospective cohort study in Tanzania,[31] although the study did not include young children and was not large enough to examine age as an interactive factor. The reasons for the interaction we found are unclear, although the protective features of fetal haemoglobin or fewer comorbid causes of anaemia (eg, chronic malnutrition or HIV) among younger children could be important.[6]

Almost half of the children enrolled in this study had axillary temperatures between 36·5°C and 37·5°C. Higher temperature was associated with reduced mortality after discharge; those with temperatures higher than 39°C had an aRR of 0·4 (95% CI 0·2–0·7). Furthermore, as children grew up, those who died tended to have lower temperatures (<36·5°C) at hospital admission than those who did not die. These observations are based on predictive axillary surface temperatures, and whether true core temperatures would differ in their association with mortality after discharge and interaction with age is unclear. Together, these findings indicate the need for a more granular understanding of how temperature relates to suspected sepsis.

Although the associations of axillary temperature and haemoglobin concentration with risk of mortality increased with age, the associations of weight-for-age and BMI-for-age Z scores with risk of mortality decreased with age. Those who were severely underweight were at increased risk of death after hospital discharge across all age strata, but the association between moderately reduced weight-for-age Z scores (–2 to –3) and risk of mortality largely disappeared at older ages. A similar observation was noted in an analysis after discharge from a surveillance programme in Kenya examining risk factors for children aged 5–12 years; only severely underweight children had an increased risk of death.[32]

Of concern are the high proportion of deaths after hospital discharge (>60%) that occurred in the community. Similar proportions of community deaths have also been observed in community-based death audits, although most caregivers reported having consulted a health-care provider at some point during the fatal illness.[33] These observations suggest that health-seeking fatigue over time might be a key factor in community deaths. A nested Kenyan sub-study within the CHAIN Network highlighted the often long and complex treatment pathways that acutely ill children navigate; intersecting vulnerabilities at individual, household, and facility levels frequently delay and prevent timely and quality care, often resulting in poor outcomes.[34] A previous analysis of deaths after hospital discharge in Uganda found that, among those who died at home, 90% considered seeking care but could not do so. This was due to various constraints, including financial limitations, lack of transportation, and sudden illness onset.[35] Although disentangling the causal complexity of deaths after discharge is difficult, reducing barriers to accessing existing care in a timely way is clearly important. Improving communication and transportation linkages between facilities and providing scheduled follow-up within communities, especially among children vulnerable to recurrent illness and death, are important strategies that could improve outcomes after hospital discharge.[36]

Facilities across a range of locations in Uganda were involved in enrolment during this study, including both rural and urban populations, providing a reasonable representation of the national Ugandan paediatric population outside the capital city of Kampala. However, this study has some important limitations. First, the study was largely exploratory and included a substantial number of analytical comparisons. Many variables measured overlapping associations, especially variables related to sociodemographic determinants of health. Additional studies are required to substantiate many of these results, and, if relevant, should include adjustments for possible confounding variables. In particular, our inclusion criteria, which were chosen to be generalisable, required only that children had a suspected infection according to the admitting medical team and were admitted to hospital. These two criteria alone suggest that approximately 90% of the children included in this study had sepsis according to the IPSCC definition.[15] Second, the study was conducted at sites that were largely rural or semirural. Large urban settings are likely to have unique contextual issues compared with rural areas, especially availability of care. However, this could also be a strength, as much of the previous literature has focused on urban settings. Third, the study was conducted in a single country. Although the results largely reflect studies conducted in other countries, its geographical limitation could affect its external validity. Finally, as this was an observational study, we cannot exclude the possibility that unmeasured variables could influence mortality after hospital discharge. Our analyses here were meant to describe the population who died, but subsequent casual analyses with these data might be subject to unmeasured confounding.

Paediatric mortality in the context of suspected sepsis is a common occurrence during the first 6 months after hospital discharge, necessitating a robust response among clinicians, researchers, and health policy leaders. In this study, we found that more than half of these deaths occurred during the first month after discharge; half occurred at home and a fifth occurred in-transit to care. Mortality after discharge was associated with several risk factors including anthropometric indices, sociodemographic characteristics obtained at admission, and discharge

circumstances. These findings might help to guide the allocation of additional resources to improve the hospital-to-home transition.

Contributors

MOW, JNB, EK, AT, CB, CO, JMA, NK, JS, CPL, PML, PPM, SN, NKM, JN, and JK contributed to funding applications. MOW, EK, AT, CB, CO, JMA, NK, JS, CPL, PML, PPM, NKM, JK, and DD designed the study. MOW, EK, CK, MT, DM, and JK coordinated study implementation. SB, AT, SOS, EB, ES, CB, DD, CK, MT, and DM supervised data collection. MOW, DD, CK, MT, DM, CZ, and MK managed the data. MOW, JNB, CZ, MK, CK, and VN analysed the data. MOW, JNB, EK, AT, JMA, NK, JS, CPL, PML, PPM, SN, NKM, NW, VN, JN, and JK interpreted the data. MOW, JNB, and NW drafted the manuscript. All authors reviewed the manuscript and had full access to all data in the study, which was verified by MOW, JNB, CK, JK, DD, CZ, and VN. All authors have approved the final manuscript and accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Study materials including the study protocol, consent form, data collection tools, de-identified participant data, data dictionary, and the analysis code will be available with publication on request to the corresponding author or through the published protocol and dataset. Owing to the sensitive nature of clinical data, access to the de-identified data is granted on a case-by-case basis and will require the signing of a data sharing agreement.

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