Post-Discharge Morbidity and Mortality in Children Admitted with Severe Anaemia and Other Health-conditions in Malaria-Endemic Settings in Africa: A Systematic Review and Meta-Analysis

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Abstract

Background

Severe anaemia is associated with high in-hospital mortality among young children. In malaria-endemic areas, surviving children also remain at increased risk of mortality for several months after hospital discharge. We aimed to compare the risks of morbidity and mortality among children discharged from hospital after recovery from severe anaemia versus other health conditions in malaria-endemic Africa.

Methods

We conducted a systematic review and random-effects meta-analyses of the mortality and re-admission risks in the first six months post-discharge among African children aged <15 years admitted with severe anaemia or other health conditions.

Findings

Twenty-seven studies were included. For recently discharged children following hospital admission with severe anaemia, the all-cause mortality by six months was higher than during the in-hospital period (N=5, Mantel-Haenszel odds ratio=1·72, 95% CI 1·22-2·44, p=0·0001, I^2=51·5%) and more than two times higher compared to children previously admitted without severe anaemia (N=4, Relative Risk [RR]=2·69, 1·59-4·53, p<0·0001, I^2=69·2%). Readmissions were also more common in children admitted with severe anaemia compared to children admitted with other conditions (N=1, RR=3·05, 1·12-8·35, p<0·0001). Children admitted with severe acute malnutrition (regardless of severe anaemia) also had a higher 6-month post-discharge mortality than those admitted for other reasons (N=2, RR=3·12, 2·02-4·68, p<0·0001, I^2=54·7%). Other predictors of post-discharge mortality included discharge against medical advice, HIV, bacteraemia and hypoxia.

Interpretation

In malaria-endemic Africa, children hospitalised with severe anaemia and severe acute malnutrition are at increased risk of mortality in the first six months post-discharge compared to children admitted with other health conditions. Improved strategies are needed for the management of these high-risk groups during the post-discharge period.

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Research in Context

Evidence before this study

Severe anaemia is a major cause of morbidity and mortality in children in malaria-endemic sub-Saharan Africa. Post-discharge mortality after the management of severe anaemia and other health conditions has been shown in some studies to be similar to or higher than in-hospital mortality. The extent of the problem has not been quantified. We searched PubMed, SCOPUS, EMBASE, Web of Science, and Cochrane CENTRAL from inception to November 30, 2020, without language restrictions, for cohort studies and randomised controlled trials. We scanned reference lists of identified articles and requested more information from authors where feasible. There are few studies that have analysed post-discharge morbidity and mortality in children <15 years in Africa. We identified one systematic review of the post-discharge mortality in developing countries, but this did not include a meta-analysis. The review concluded that studies consistently found post-discharge mortality to be similar, or to exceed, in-hospital mortality.

Added value of this study

To our knowledge, this is the first meta-analysis that compares the post-discharge mortality and morbidity burden in malaria-endemic Africa for different health conditions. The available information confirms that children who were recently hospitalised with severe anaemia or severe acute malnutrition are at excess risk of mortality during the first six months post-discharge compared to children admitted for other health conditions. Among the children recently admitted with severe anaemia, the mortality is higher during the first six months post-discharge than during the in-hospital period.

Implications of the available evidence

The post-discharge period is a well-recognised risk period for children with severe acute malnutrition for which appropriate follow-up and management strategies exist. However, it is largely unaddressed for children hospitalised with severe anaemia. Improved post-discharge strategies directed at this high-risk paediatric population need to be developed.

Introduction

Substantial progress has been made in reducing all-cause child mortality globally in the past decade, but about 1 in 13 children in sub-Saharan Africa still die before their fifth birthday.[1] Severe anaemia and malaria are major contributors to morbidity and mortality in malaria-endemic areas of Africa.[2,3] Severe anaemia alone accounts for 2-29% of all paediatric hospitalisations,[4-6] and 4 to 10% of these children die while admitted in hospital.[7-9] The aetiology of severe anaemia is multifactorial and includes nutritional causes,[10,11] and acute and chronic infections such as malaria, tuberculosis, human immunodeficiency virus (HIV), bacteraemia, and hookworm infestations.[12]

Recent studies among children with severe anaemia have focused on interventions to reduce in-hospital mortality.[13-15] However, it is increasingly recognised that the high risk of all-cause mortality continues after hospital discharge,[16-19] with up to 33% of the children dying or being readmitted within the first six months post-discharge.[7,20] Children admitted with severe anaemia are believed to constitute an especially vulnerable group of seriously ill children that remain at high risk after hospitalisation due to a wide range of factors, including clinical, epidemiological and nutritional factors.[12,18]

The post-discharge period is a well-recognised risk period for children with severe acute malnutrition,[21,22] but is less studied in children with severe anaemia. Quantification of the burden of post-discharge mortality and morbidity in children recently recovered from severe anaemia is important for the development of post-discharge management strategies. To aid in this process, we conducted a systematic review and meta-analysis to compare the pooled risks of post-discharge mortality and readmissions among children admitted with all-cause severe anaemia versus other health conditions without severe anaemia in malaria-endemic areas of Africa. We also compared in-hospital against post-discharge mortality.

Methods

Search strategy and selection criteria

This analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[23] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO-CRD42017079282).

Search strategy

We identified eligible studies by performing a literature search using a combination of search terms (Supplement 1, page 3) in PubMed, SCOPUS, EMBASE, Web of Science and Cochrane CENTRAL from inception to November 30, 2021, without language restrictions. We identified other relevant studies by scanning reference lists of all identified articles and searching in Google and Google Scholar. Where necessary, authors of published studies were contacted up to three times for further information.

Eligibility criteria

Prospective or retrospective cohort studies and control arms of individually randomised-controlled trials (RCTs) were eligible for inclusion if they (i) presented original data with or without comparator groups; (ii) included children <15 years of age admitted with severe anaemia or other health conditions such as malaria, pneumonia, diarrhoea, malnutrition, HIV, alone or in combination with severe anaemia; (iii) defined the duration of the post-discharge follow-up; and (iv) were conducted in African countries that are malaria-endemic according to the World Malaria Report 2020.[24] The definition of severe anaemia followed

the definition used in the source studies (e.g., haemoglobin <5 or <6 g/dL, clinical requirement for blood transfusion). Severe acute malnutrition in children was defined as mid-upper arm circumference <115 mm, or a weight-for-height/length <–3 Z-scores of the WHO Child Growth Standards median.

Studies or sub-groups were excluded if they (i) involved admissions for sickle cell anaemia, malignancies, surgery, or road accidents and other trauma cases or (ii) reported follow-up data that were combined with the in-hospital period.

Study selection and data extraction

Two independent reviewers (TKK and ATM) screened titles, abstracts and full texts of the identified articles and agreed on the final eligibility. Any disagreement between the two reviewers was resolved through consensus or after consultation with a third reviewer (FOtK).

TKK and ATM independently extracted the data using a standardised form and database. If required, additional information was obtained from the authors. In trials or other comparative studies where interventions were provided, only the data from the control groups that received the standard of care were included.

Quality assessment

The Cochrane Collaboration's tool was used to assess the quality and risk of bias of clinical trials.[25] For observational and cohort studies with comparison groups, we used the Newcastle Ottawa Scale.[26] For cohort studies without comparison groups, we used a modified version of the Newcastle Ottawa Scale that omitted the comparability criteria and the section on "selection of the non-exposed cohort" in the "selection criteria".

Data analysis

Two primary outcome measures were used: all-cause death or all-cause readmissions by six months post-discharge. Secondary outcomes are defined in Supplement 2 (page3). The post-discharge follow-up period varied from 28 days to 5 years. Follow-up data beyond one year was truncated to <12 months for analysis. The method used to address loss-to-follow-up was based on the method provided in the source study. If survival analysis was used, children were censored at the time they were lost before completing six months follow-up. In studies reporting risk, children lost to follow-up were excluded from the denominator.

Data were analysed using STATA version 14·0 (Stata Corporation, College Station, TX). DerSimonian and Laird random-effects meta-analyses were used to generate pooled relative risks (RR). The Mantel-Haenszel odds ratio (MHOR) for paired binary outcomes was used to compare in-hospital and post-discharge mortality rates.[27] Hazard ratios (HR) were used to generate pooled effect estimates where the original measures were presented as HR.

Heterogeneity was expressed using the I^2 statistic and categorised as low, moderate, substantial and considerable if the I^2 values ranged between 0-40%, 30-60%, 50-90%, and 75-100%, respectively.[28] As part of sensitivity analysis, the pooled effect estimates using fixed-effect models (Mantel-Haenszel) are provided in the forest plots. We intended to perform sub-group and sensitivity analyses to determine the influence of study quality, study region, age, and malaria transmission intensity, but this was not possible due to the small number of studies and lack of heterogeneity in study quality. We aimed to use funnel plots to assess possible publication bias and small-study effects where ten or more studies were included in the meta-analysis. However, this was not possible due to the small number of independent studies that contributed.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search identified 2,930 articles. After removing duplicates and screening of titles and abstracts, 82 full-text articles were further evaluated, of which 27 were eligible, including 22 cohort studies[16,18,19,22,29-46] and 5 RCTs[47-51] (Figure 1 and Table S1). The studies were published between 1987 and 2021 and conducted in Kenya (nine), Malawi (four), Uganda (five), Guinea-Bissau (two), Democratic Republic of Congo (two), Tanzania (three), The Gambia (one), Zambia/Zimbabwe (one) and Mozambique (one). The main diagnosis on admission, henceforth referred to as 'main health condition', included severe anaemia (nine studies), malaria (three), pneumonia (four), malnutrition (three), diarrhoea (one); there were ten other studies in which the main health conditions were not specified (unspecified health condition). The post-discharge mortality ranged from 1 to 39% based on the total post-discharge follow-up time (Table S1). The average (mean, SD) and median (IQR) duration of follow-up for the primary outcome varied between health conditions (Table S2). Three RCTs were scored as low risk of bias and two open-label trials as unclear risk of bias (Table S3). Twenty-one cohort studies were scored as good quality and one as poor (Table S4 and Table S5).

Post-discharge mortality by health condition at enrolment
A meta-analysis of the post-discharge mortality from 20 studies showed that the crude risk of post-discharge all-cause mortality by six months ranged from 2·3%-15·9%, 2·8%-27·1%, 0·7%-9·9%, 2·3%-5·6% and 1·1%-11·8% for severe anaemia, malnutrition, malaria, pneumonia, and unspecified health conditions, respectively (Figure *2*). The 12-month post-discharge mortality by health condition (23 studies) is shown in Figure S1. Because there was considerable heterogeneity in the post-discharge mortality between (I^2=95·4%) and within health condition groups (I^2>70% for all), a pooled summary risk obtained by meta-analysis was not calculated.

Among these 22 studies, six reported enough detail to allow direct comparisons by admission health condition (Figure 3, Table S6). The 6-month post-discharge mortality among children previously admitted with severe anaemia was 2·69 times higher compared to children previously admitted without severe anaemia during the same study period and in the same hospitals (N=4 studies, RR=2·69, 1·59-4·53, p<0·0001, I^2=69·2%). Severe malnutrition was also associated with higher post-discharge mortality (N=2, RR=3·12, 2·07-4·68, p<0·0001, I^2=54·7%). On the other hand, the post-discharge mortality among children admitted with severe pneumonia, malaria, and unspecified health conditions was similar or lower compared to children admitted for other reasons. Similar trends were observed by 12 months post-discharge (Figure S1, Figure S2).

When the analysis was repeated, but now excluding children with severe acute malnutrition from the comparator group (*post-hoc*), the RR for 6-month post-discharge mortality for children with severe anaemia relative to other children was 2·30 (N=2, 1·11-4·78, p<0·025, I^2=88·2%. There were insufficient data for a similar comparison by twelve months. For malnutrition, the RR was 3-fold higher by six months when compared to a reference that

excluded the children with severe anaemia (N=2, RR=3·26, 1·62-6·56, p=0·001, I^2=83·0%). This was similar by twelve months (N=2, RR=3·26, 2·47-4·30), P<0·0001, I^2=0·0%) (Table S6).

Children who had both severe anaemia and malaria (i.e., severe malarial anaemia) had a lower risk of post-discharge mortality than children with severe anaemia without evidence of malaria (N=2, RR=0·71, 0·48-0·94, p<0·0001, I^2=0·0%) (Figure S3).

Post-discharge versus in-hospital mortality

During the in-hospital period, 5·6% (2,369/41,945) of children died (N=19), ranging from 0·4%-13·0% for severe anaemia and 3·0%-23·2%, 1·0%-15·1%, 2·7%-11·5%, and 1·8%-12·5% for acute malnutrition, malaria, pneumonia, and unspecified health conditions respectively. Due to high inter-study heterogeneity (I^2=96·5%), pooled summary risks were not calculated (Figure S4).

Thirteen cohort studies involving a total of 23,600 admissions reported both in-hospital and post-discharge mortality. Overall, across all health conditions pooled, the mortality post-discharge by six months was not different from in-hospital mortality (MHOR=0·92, 0·66-1·28, p=0·625, I^2=92·1%). However, there was considerable heterogeneity within and between health condition sub-groups. Among children admitted with severe anaemia, the odds of mortality were consistently higher in the post-discharge period than during hospitalisation (N=5, MHOR=1·72, 1·22-2·44, p=0·002, I^2=51·5%). This was not observed for any of the other health conditions (Figure *4*).

Post-discharge mortality vs mortality in the community

Six prospective follow-up studies showed that the mortality during the first six months post-discharge was nearly 5-fold higher in recently hospitalised children (any health condition), relative to otherwise healthy children from the community (N=6, RR=4·88, 2·73-7·03, p<0·0001, I^2=0·0%), with the greatest difference among children recently recovered from severe anaemia (Figure S5).

Other risk factors for post-discharge mortality

Eleven studies analysed other potential risk factors for post-discharge mortality. Risk factors significantly associated with post-discharge mortality in some of these studies included: discharge against medical advice, hypoxia (SPO_2<90%), bacteraemia, low haemoglobin on admission, younger age, previous hospitalisation, positive maternal HIV status, poor anthropometric measurements, reduced consciousness, proteinuria, absence of malaria parasites on admission, and admission with a chronic disease. HIV positivity was associated with an increased risk of post-discharge mortality in two studies before the widescale introduction of antiretroviral therapy (ART) and in six studies after the introduction of ART (Figure S6 and Supplement 3, page 3).

Post-discharge readmission

Eleven studies reported post-discharge readmissions for periods ranging between 3 to 18 months with wide variations in the reported readmission risk (Table S1). The crude proportion of children readmitted at least once by six months was 17·3% (897/5,188), ranging from 3·1% to 30·6%, based on seven studies.[18,22,38,48-51] Readmissions for severe anaemia and non-anaemia by six months post-discharge were 21·8% and 7·2% respectively in these six studies. Only one study allowed for a direct comparison of readmission risk between severe anaemia and other health conditions and reported a three-fold (N=1, RR=3·05, 1·12-8·35) increased risk by six months.[18]

Sensitivity analysis

Because of the observed variation in the duration of follow-up between health conditions (Table S2), a *post-hoc* sensitivity analysis was conducted, excluding four studies that had <6 months follow-up. Similar conclusions could be drawn for severe anaemia and severe acute malnutrition from the sensitivity analysis (N=10 studies, Figure S7) compared to the full data set (N=13 studies, Figure 3) regarding the excess risk of post-discharge mortality relative to other health conditions. Similarly, the conclusions remained unaffected for severe anaemia when comparing in-hospital vs post-discharge mortality (N=5 studies, Figure 4 vs N=4 studies, Figure S8). However, for severe acute malnutrition, the difference between in-hospital and post-discharge mortality was greater when the analysis was restricted to studies with at least six months follow-up (N=1) (MHOR=1·83, Figure S8) than with the full sample of four studies (MHOR=0·93, Figure 4).

Discussion

To our knowledge, this is the first systematic review and meta-analysis comparing the risk of post-discharge mortality and readmission in malaria-endemic Africa by health condition on admission. Children discharged from hospital after recovery from severe anaemia or severe acute malnutrition were 2·7 and 3·1 times more likely to die from any cause during the first six months post-discharge than children previously admitted with other health conditions. By contrast to children admitted with malnutrition or other health conditions, children with severe anaemia were also more likely to die in the six months post-discharge than during hospitalisation. Readmissions during this period were also more likely among children previously admitted for severe anaemia than children admitted for other reasons, but this was based on only one study. Although there was substantial variation in study designs, these findings indicate that in malaria-endemic countries in Africa, children admitted with severe anaemia and severe acute malnutrition remain at a high risk of mortality in the first few months post-discharge.

Although the post-discharge mortality was highest among those admitted with severe anaemia or malnutrition, this review also showed that any hospitalised child, regardless of the health condition on admission, was at a nearly 5-fold higher increased risk of dying within six months post-discharge than the apparently normal, non-hospitalised children from the same community. These findings agree with a recent systematic review of all-cause post-discharge mortality among the general paediatric population, which indicated a significant global burden of post-discharge mortality, especially in low-income countries.[17]

Recently the term “post-hospital health condition” was proposed, which refers to an acquired, transient condition of vulnerability in recently hospitalised, mostly elderly patients in the United States of America, resulting in a period of generalised risk for myriad adverse health events not necessarily linked to the original illness. During this period, the patient is not only recovering from the initial acute illness but also suffers continued physiological and immunological impairment due to the initial insult and other stressors following hospitalisation.[52]

We were unable to analyse the reasons for the high post-discharge mortality or readmission rates observed in children with severe anaemia because of the lack of details available from the source studies about the cause of readmissions or deaths. These are likely to reflect the complex multifactorial nature of the aetiologies of anaemia in this setting, which includes nutritional, environmental, biological, socio-behavioural, and genetic factors.[53] Explanations

for high post-discharge mortality may include continued exposure to the same risk factors in the community that resulted in the initial admission and possible delays in seeking appropriate care due to local beliefs and perceptions about severe anaemia.[54] Although insufficient details were available to allow an analysis of HIV status as a standalone condition on admission, HIV-positive children were at a 1·4 to 6·5-fold increased risk of post-discharge mortality compared to HIV-negative children. Recurrent malaria infections have also been reported as risk factors for the recurrence of severe anaemia among these children.[18,19,44,48,50]

In contrast to severe anaemia, malnutrition is recognised as a major risk factor for post-discharge mortality in resource-poor countries, with guidelines for further follow-up and care at home and periodic monitoring to avoid relapse.[21,55,56] Malnourished children were not only at increased risk of post-discharge mortality compared to other children, but the co-existence of severe undernutrition was also a significant contributor to post-discharge mortality among children recently admitted with other health conditions, including those with severe anaemia.[22,30,35,42] Many undernourished children in resource-poor settings have underlying medical/co-morbid conditions either directly causing, contributing to, or complicating malnutrition.[14]

It was of interest to see that children with severe malaria *per se* (e.g., cerebral malaria without severe anaemia) had lower post-discharge mortality than children with severe anaemia. We also found a significantly lower risk of post-discharge mortality among children with severe malarial anaemia compared to children with severe anaemia without malaria. It is possible that the attribution of multiple and chronic causes of severe anaemia such as micro-nutrient deficiencies or chronic infections such as tuberculosis and HIV was greater among the children without malaria. If so, they would require multiple and long-term interventions post-discharge. This might not be the case for children where malaria was the main cause of severe anaemia, in particular if the initial event was successfully treated with blood transfusion and effective antimalarials. Alternatively, the in-patient population treated for 'severe' malaria may reflect a heterogeneous group of patients as in many countries, large numbers of uncomplicated malaria patients are admitted as in-patients to health facilities.[57]

Although in-hospital severe malaria was not a major risk factor for post-discharge death, in highly endemic areas, malaria may become an important risk factor for readmissions or mortality post-discharge in all groups. Prolonged malaria infection causes dyserythropoiesis, which may result in bone marrow suppression and may be prolonged in children who become reinfected or in whom the initial infection is not cleared, or not recognised and therefore not treated.[3,44,58,59] In children initially admitted with severe anaemia who have prolonged dyserythropoiesis and/or bone marrow suppression, the benefit of blood transfusion(s) during hospitalisation may be too short-lived to allow for full haematological recovery. These children may develop rebound severe anaemia and poor immunological responses to bacterial and other infections.

Other risk factors significantly associated with post-discharge mortality irrespective of the initial exposure condition included hypoxia, bacteraemia/sepsis, jaundice, hepatomegaly, splenomegaly, prolonged hospitalisation, lower socio-economic status, reduced consciousness on admission (Blantyre coma scale <5), delay in seeking care, history of previous hospitals admissions, young age, and discharge against medical advice.

These findings support the need for management strategies for recently discharged children, especially those with severe anaemia and severe acute malnutrition in malaria-endemic areas of Africa. Improved diagnosis for the underlying causes of severe anaemia is also merited. Post-discharge interventions that have been shown to be effective include preventive zinc supplementation to reduce morbidity and mortality due to diarrhoea and pneumonia[60] and prophylaxis with co-trimoxazole to reduce morbidity and mortality in HIV-positive individuals.[61] More recently, neither three months of enhanced supplementation with multivitamin multimineral supplement or co-trimoxazole prophylaxis improved 6-month survival versus iron and folate treatment.[49] However, three months of post-discharge malaria chemoprevention (PMC) with artemether-lumefantrine among children admitted with severe malaria anaemia prevented 41% of deaths or readmissions during the 12 week intervention period in a trial in Malawi,[50] and 70% using dihydroartemisinin-piperaquine in a recent trial in Kenya and Uganda which recruited children with all-cause severe anaemia.[48] Policy guidelines for the post-discharge management of severe anaemia in children living in malaria-endemic areas of Africa are needed urgently.[62]

There are important limitations to this type of secondary analysis. Some limitations are common to many meta-analyses. First, there was considerable variation in the duration and/or reporting of follow-up data, e.g., some studies followed children only for one month, whereas others followed them for much longer than six months but did not report results by six months and could thus not contribute to our meta-analysis. For this reason, a *post-hoc* sensitivity analysis was conducted that excluded four studies with <6 months follow-up, which confirmed the excess post-discharge mortality in children with severe anaemia relative to other health conditions or relative to in-hospital mortality. A second limitation is the variations in the design of observational studies and RCTs and their reporting, and in the prevalence of various background causes of mortality contributed to substantial observed heterogeneity. Third, few studies reported both in-hospital and post-discharge mortality, and few studies reported post-discharge mortality by admission health condition. Those that did had relatively modest sample sizes and events. Fourth, the results of random effect models based on a small number of studies should be interpreted with caution because reliable estimates of the between-studies variance (and thus the confidence interval), summary point estimates, and the dispersion effect are difficult to obtain.[63] Fifth, we could not analyse the causes of post-discharge deaths due to insufficient details reported. Sixth, we were unable to assess small-study effects or publication bias because of the small number of studies per health condition and the likely presence of heterogeneity and/or true small study effects for meta-analysis of observational studies. Seventh, we were unable to assess the effect of any residual confounding by comparing crude and adjusted meta-analyses due to the limitations of the data reported. Lastly, included studies that recruited children with severe anaemia did not report on the aetiology of anaemia on admission. Therefore, we could not determine the cause-specific severe anaemia mortality burden in-hospital or link the aetiology to post-discharge mortality burden. The variation in reporting the risk factors for post-discharge mortality and scarcity of data on the causes of post-discharge mortality are important considerations for future research to develop a comprehensive post-discharge management plan.

Conclusion

This review confirms that children <15 years of age who are recently discharged from hospital after recovery from severe anaemia or severe malnutrition are at excess risk of mortality during the first six months post-discharge compared to children admitted for other

causes such as severe malaria. There is a need to develop post-discharge management strategies for these high-risk groups.

Article information

Contributors

TKK and FOtK conceived the idea. TKK wrote the protocol with input from ATM, AVE, SN and FOtK. TKK and ATM developed the search terms and applied them to the electronic databases. TKK and ATM reviewed all abstracts and selected full-text articles selected and assigned bias scores; FOtK served as the tiebreaker. TKK and ATM independently abstracted all the data. TKK conducted the meta-analysis with inputs from ATM, FOtK and SN. SN provided statistical support. TKK and FOtK wrote the first draft of the manuscript. All authors reviewed, revised and approved the final version of the manuscript.

Data sharing statement

All aggregated data collected during this analysis will be made available and access to data provided when a proposal has been approved by the investigators, after consideration of overlap between the proposal and any ongoing efforts. Proposals should be directed to Professor Feiko ter Kuile (feiko.terkuile@lstmed.ac.uk) and Dr Titus Kwambai (qbb5@cdc.gov) to gain access. Data requesters will need to sign a data access agreement, and the database will be transferred electronically**.**

Declaration of interests

There are no conflicts of interest to declare.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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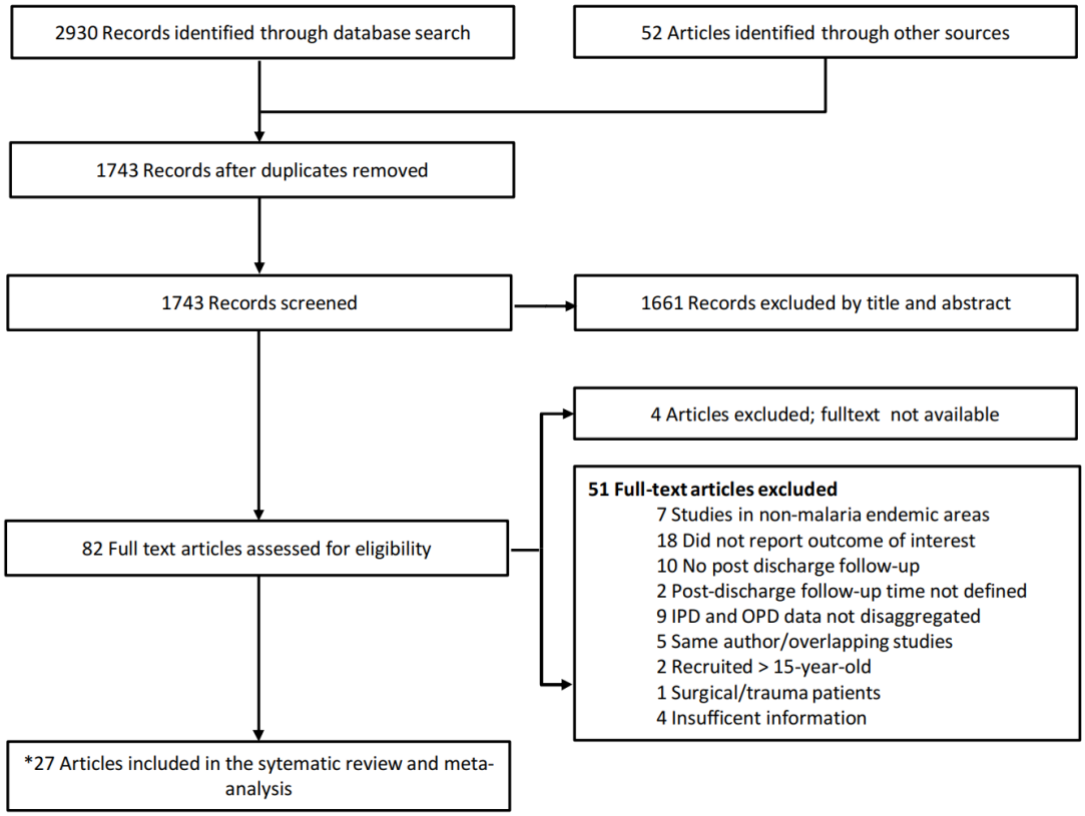
Figures

Figure 1: PRISMA Flow Diagram



IPD=in-patient department (i.e., admitted children). OPD=outpatient department. Reasons for exclusion exceed the number of articles excluded because some articles had more than one reason for exclusion.

*including a prospective follow-up study of children who were initially enrolled in a prospective case-control study[19]

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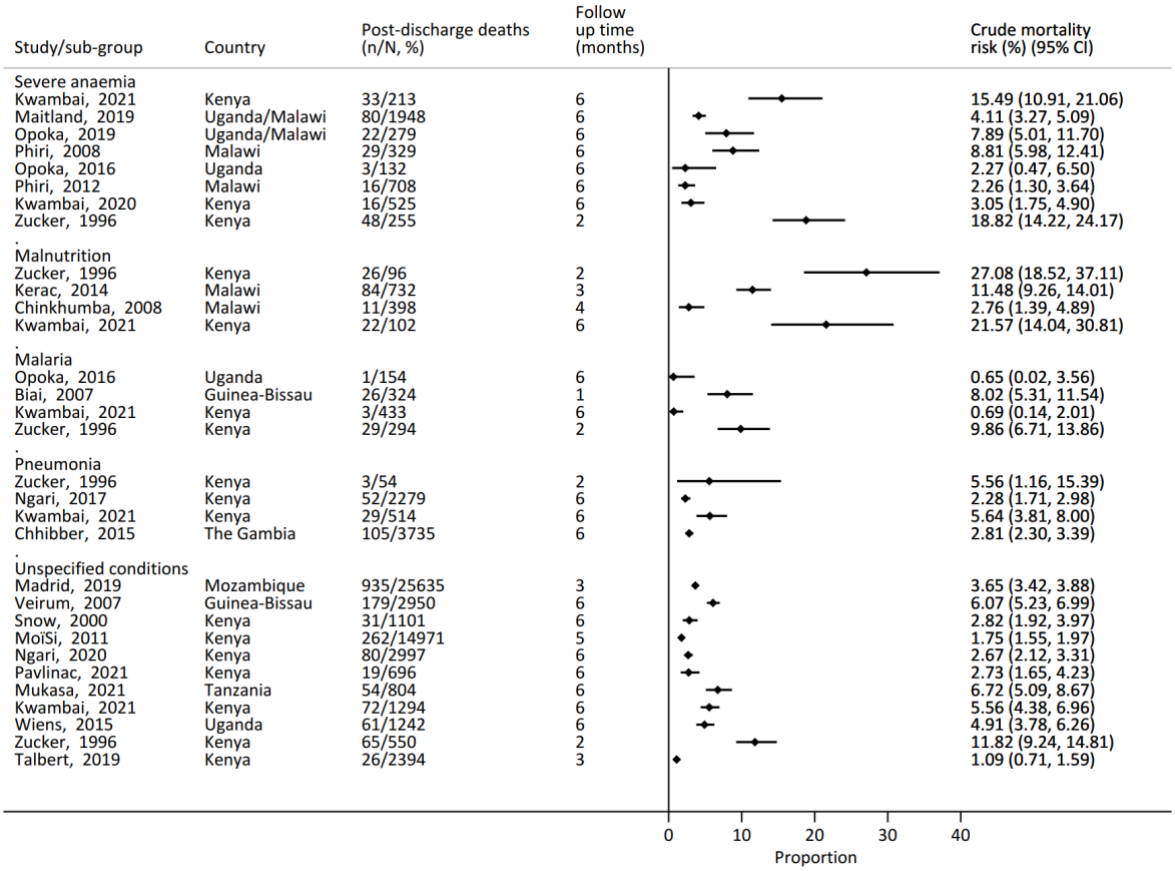
Figure 2: Crude mortality risk for any follow up period in the first six months post-discharge (all studies)



Kwambai 2021 Zucker 1996 and Opoka, 2016 are included in more than one sub-group, each representing a mutually exclusive group. The malaria studies did not include any post-discharge chemoprophylaxis groups. The summary statistics are not shown due to considerable heterogeneity (the pooled I^2 is 95·5%) between and within admission health condition groups.

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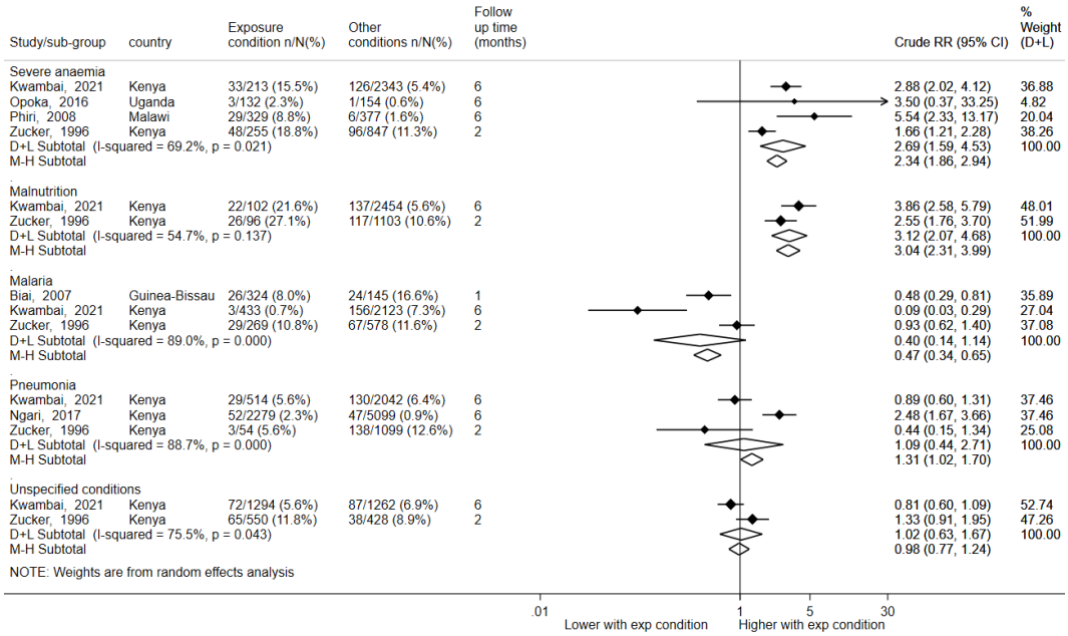
Figure 3: Relative risk of mortality by six-month post-discharge among studies reporting results by multiple health conditions



RR=relative risk. CI=confidence interval. D+L=DerSimonian and Laird random effects. M-H=Mantel-Haenszel fixed effect. Exp=exposure group Includes only studies that reported enough detail to allow direct comparisons of the post-discharge mortality by health condition among children from the same cohort study. Diamond shapes depict the pooled effect size. The crude RR is calculated by comparing the "exposure condition" vs "other conditions". For example, in the first section under "Severe anaemia", the random effects summary crude RR of 2.69 (95% CI 1.59-4.53) represents the relative risk of post-discharge mortality comparing children who were recently admitted with severe anaemia versus all other children that were recently admitted for any other conditions that excluded severe anaemia ("Other conditions"), such as severe acute malnutrition, severe malaria, severe pneumonia or other unspecified conditions). Similarly, the second section under malnutrition (summary random effects RR 3.12) represents the relative risk of post-discharge mortality comparing children who were recently admitted with severe acute malnutrition versus children that were admitted for any other conditions that excluded severe acute malnutrition. In the latter case, "Other conditions" includes children with severe anaemia, severe malaria, severe pneumonia or other unspecified conditions.

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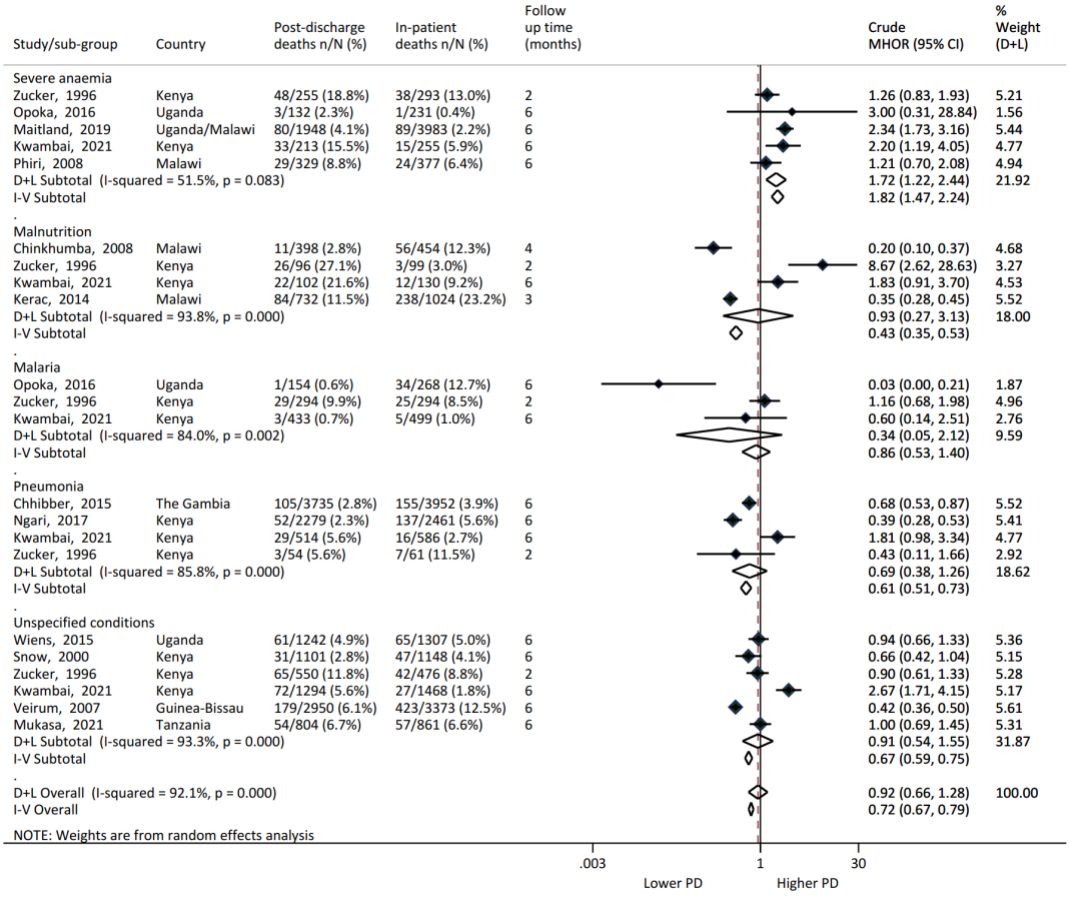
Figure 4: In-patient vs post-discharge mortality within six months by health condition on admission.



D+L=DerSimonian and Laird random effects. I-V=inverse-variance fixed-effect. MHOR=Mantel-Haenszel odds ratio. PD=post-discharge. For each study, the MHOR is obtained by comparing the number of "post-discharge deaths" vs "in-patient deaths" during the initial hospitalisation.

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Supplementary appendix

Supplement to: Kwambai et al., Post-Discharge Morbidity and Mortality in Children Admitted with Severe Anaemia and Other Health-conditions in Malaria-Endemic Settings in Africa: A Systematic Review and Meta-Analysis

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Supplemental methods

Supplement 1: Search terms used in PubMed

(((((((((child) OR childhood) OR infant) OR paediatric)) AND ((((((((((anemia) OR "severe anemia") OR "severe malaria") OR "severe malaria anemia") OR "severe malarial anemia") OR "severe malarial anaemia") OR "severe pneumonia") OR "severe malnutrition") OR diarrhea) OR sepsis)) AND (((((((death) OR admission) OR readmission) OR mortality) OR morbidity) OR survival) OR post-discharge health condition)) AND ((((((post-discharge) OR post-discharge) OR post hospitalization) OR longitudinal) OR follow-up) OR discharge follow-up)) AND ((cape verde) OR Gambia) OR Mauritania) OR guinea bissau) OR liberia) OR togo) OR sierra leone) OR benin) OR senegal) OR guinea) OR cote d'ivoire) OR mali) OR ghana) OR burkina fasso) OR niger) OR nigeria) OR zimbabwe) OR zambia) OR swaziland) OR south africa) OR namibia) OR mozambique) OR malawi) OR mauritius) OR madagascar) OR botswana) OR angola) OR egypt) OR uganda) OR tanzania) OR sudan) OR somalia) OR rwanda) OR mayotte) OR kenya) OR ethiopia) OR eritrea) OR djibouti) OR comoros) OR burundi) OR "sao tome") OR ("sao tome and principe")) OR "equatorial guinea") OR gabon) OR "central african republic") OR congo) OR chad) OR cameroon) OR "democratic republic of congo")) OR ((africa) OR sub-saharan africa))) NOT (((((((("aplastic anemia") OR "severe aplastic anemia") OR "acquired aplastic anemia") OR "Fanconi anemia") OR "megaloblastic anemia") OR "maternal anemia") OR "pregnant women") OR "sickle cell anemia").

Supplement 2: Outcome definitions

Primary outcomes

All-cause death or all-cause readmission in the first six months post-discharge

Secondary outcomes

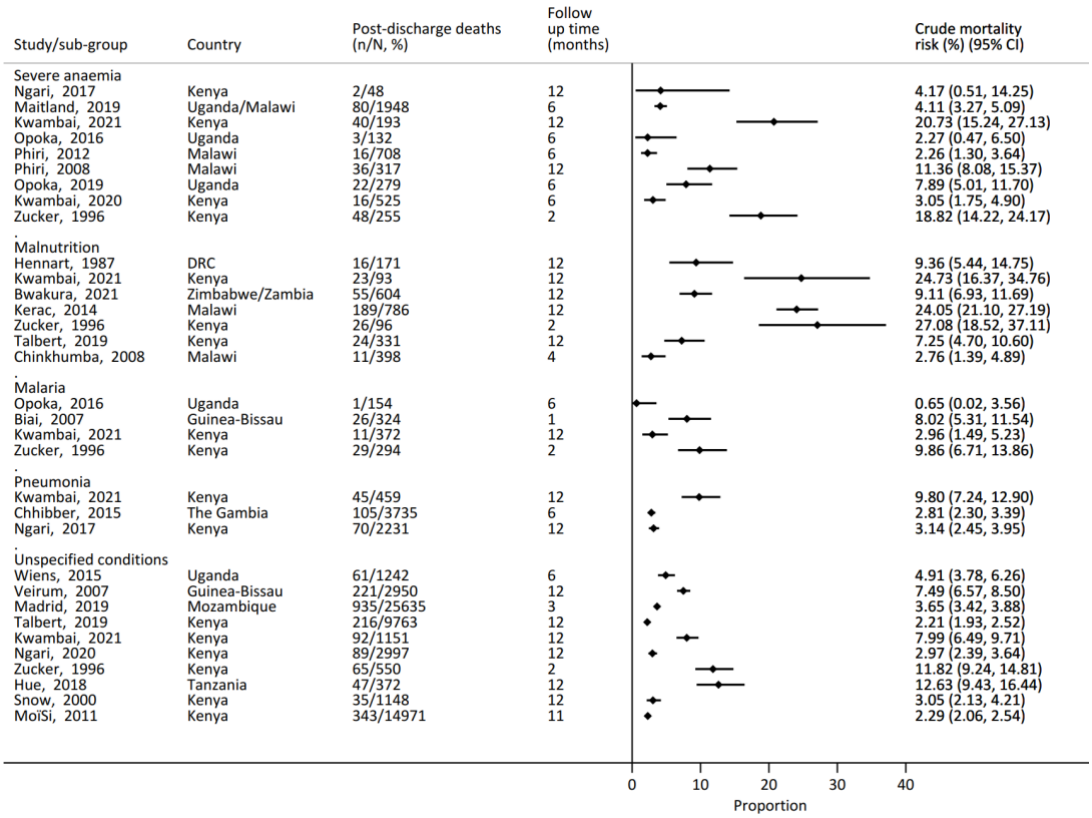
- Deaths due to severe anaemia in the first six months post-discharge
- Deaths due to health conditions other than severe anaemia in the first six months post-discharge
- In-hospital deaths due to severe anaemia
- In-hospital deaths due to health conditions other than severe anaemia
- Readmission due to health conditions other than severe anaemia

Supplement 3: Analysis of risk factors

The crude hazard ratios for other risk factors of post-discharge mortality reported in the source studies are summarised in Table S7 and Figure S6. However, no meta-analysis of these other risk factors was conducted due to differences in definitions and scales.

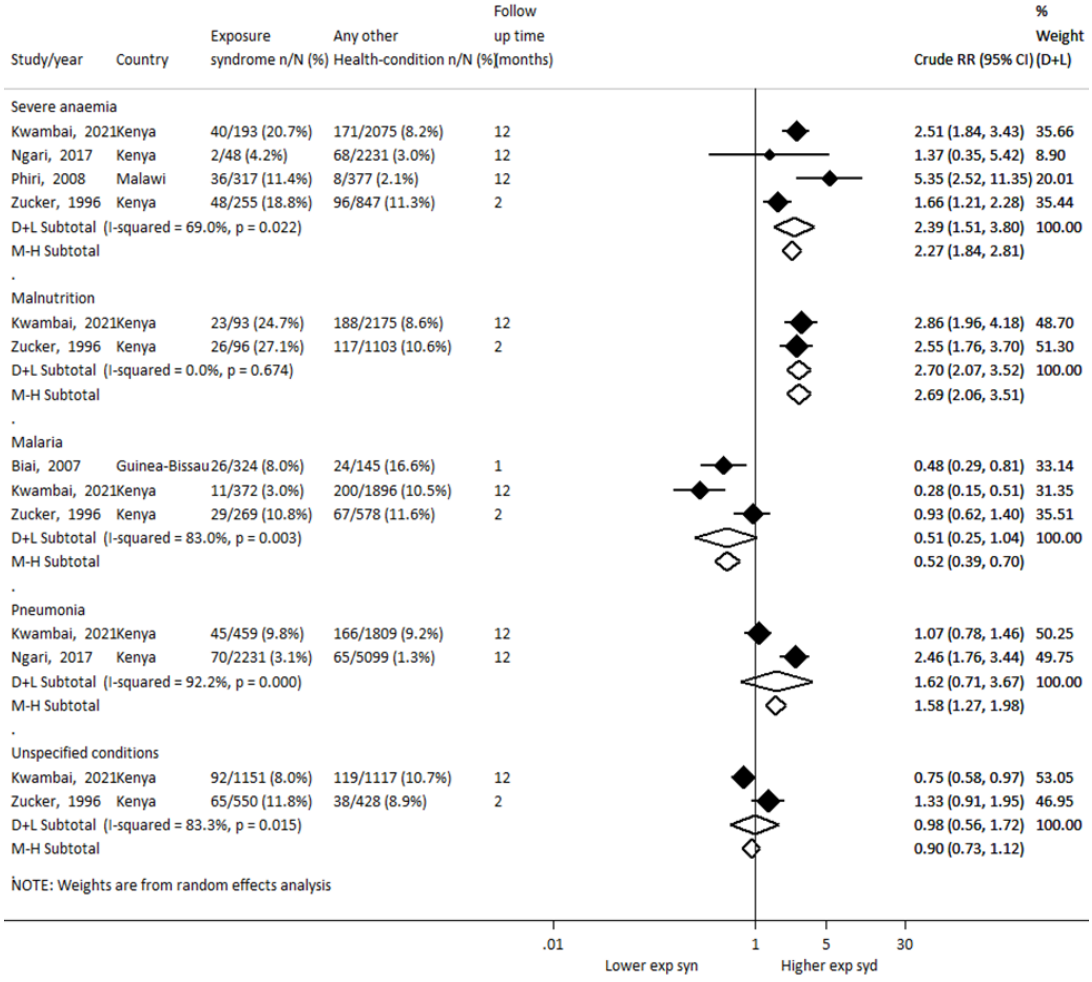
Supplemental figures

Figure S1: Mortality risk by twelve months post-discharge or earlier (all studies)



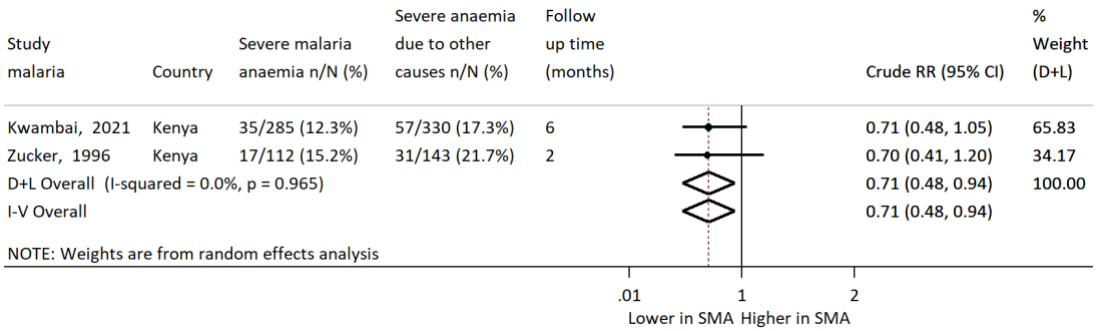
Kwambai 2021, Zucker 1996 and Opoka 2016 are included in more than one sub-group, each representing a mutually exclusive group. Due to considerable heterogeneity (the pooled I^2 is 96·6%) between and within admission health condition groups, the summary statistics are not shown.

Figure S2: Relative Risk of mortality by twelve-month post-discharge among studies reporting results by multiple syndromes



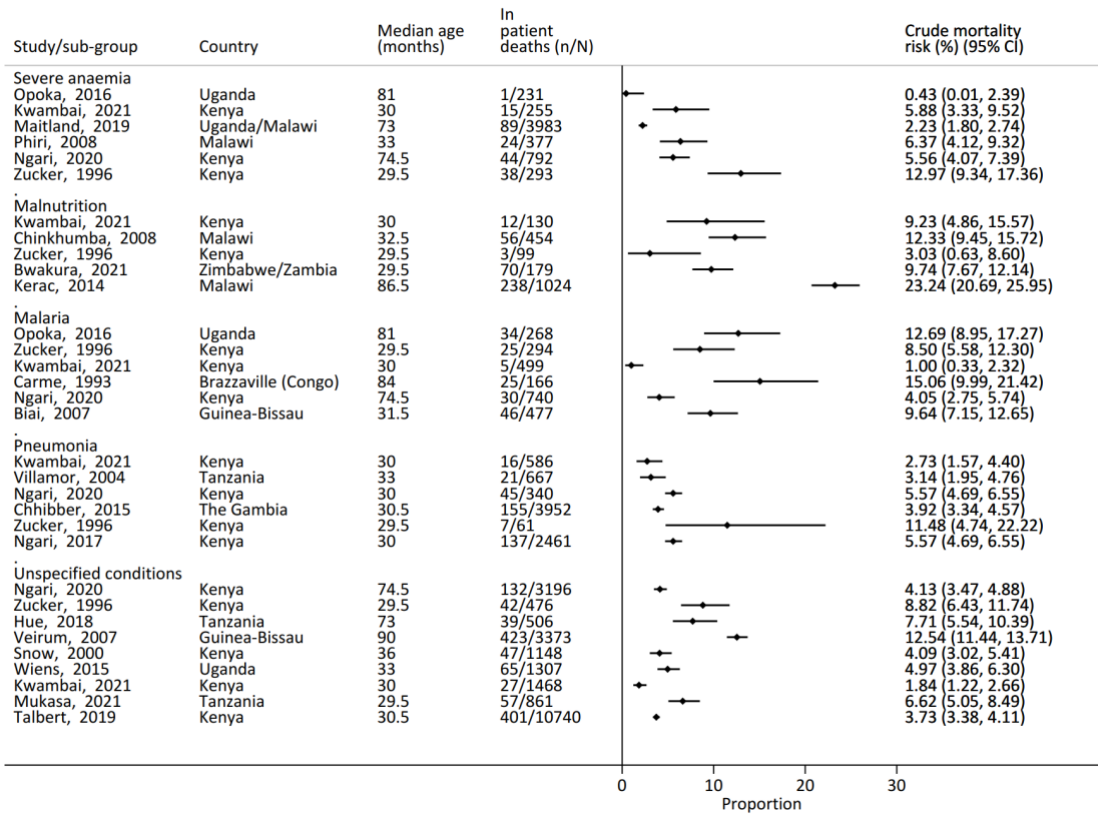
RR=relative risk. CI=confidence interval. D+L=DerSimonian and Laird random effects. M-H=Mantel-Haenszel fixed effect. Includes only studies that reported enough detail to directly compare the post-discharge mortality by health condition among children from the same cohort study.

Figure S3: Post-discharge mortality between severe malaria anaemia vs severe anaemia due to other causes.



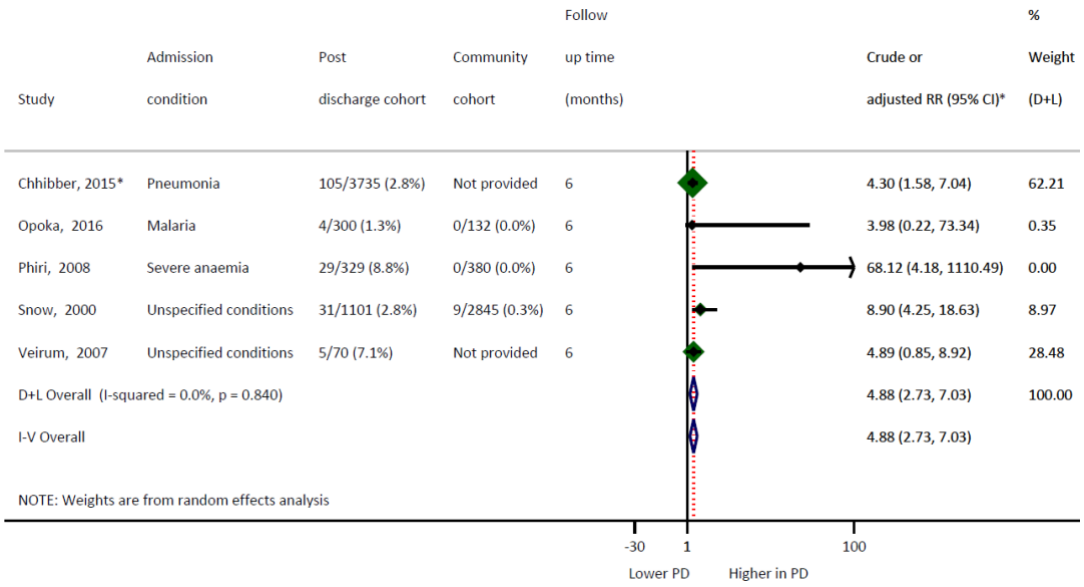
RR=relative risk. CI=confidence interval. D+L=DerSimonian and Laird random effects. I-V=inverse variance fixed effect. SMA=severe malarial anaemia.

Figure S4: Mortality risk in-hospital by health condition.



Kwambai 2021, Zucker 1996 and Opoka 2016 are included in more than one sub-group each representing a mutually exclusive group. The summary statistics are not shown due to considerable heterogeneity (The pooled I^2 is 96·9%) between and within admission health condition groups.

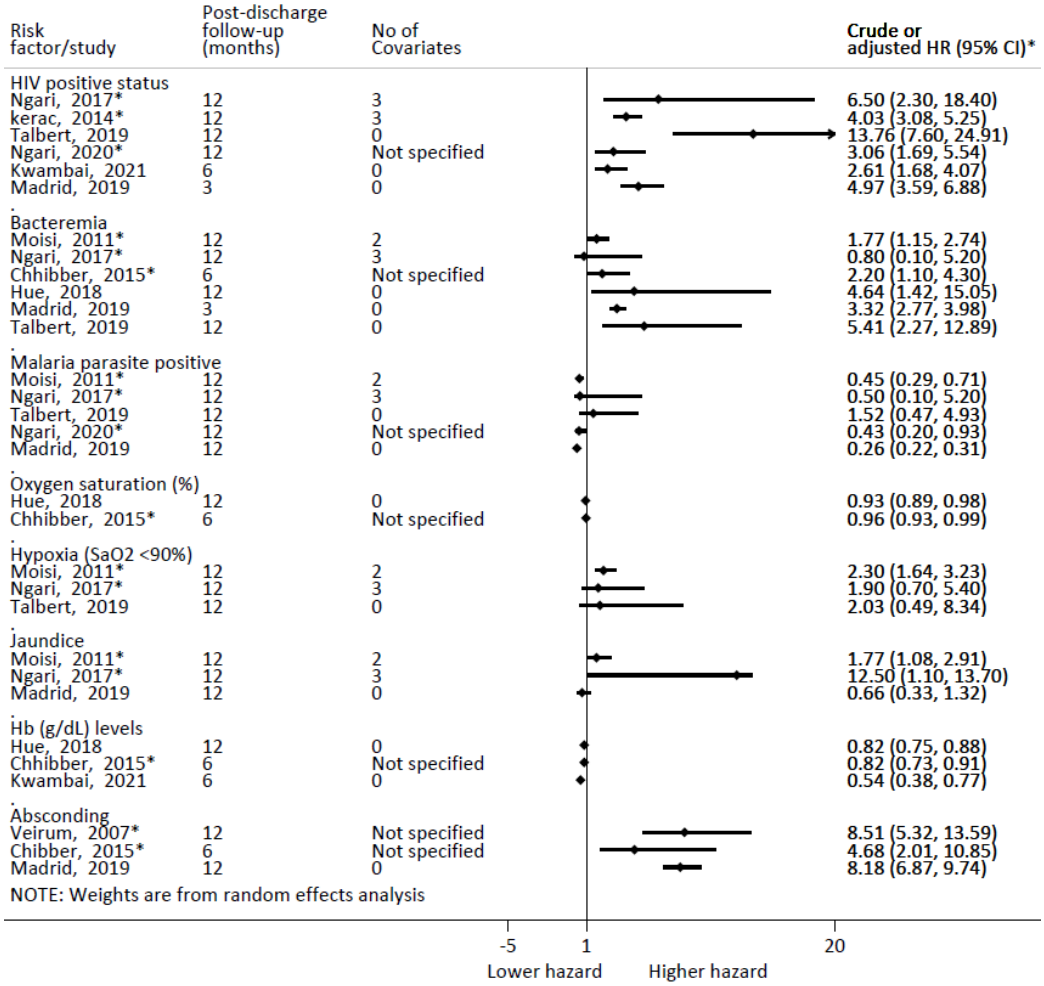
Figure S5: Mortality within six months post-discharge versus community cohorts



RR=relative risk. CI=confidence interval. D+L=DerSimonian and Laird random effects. I-V=inverse variance fixed effect. PD=post-discharge. The data columns towards the left of the forest plot represent n/N (%) for these data points.

*Adjusted effect estimates were used for this data point because the crude effect estimate, or crude data (n/N) were not available

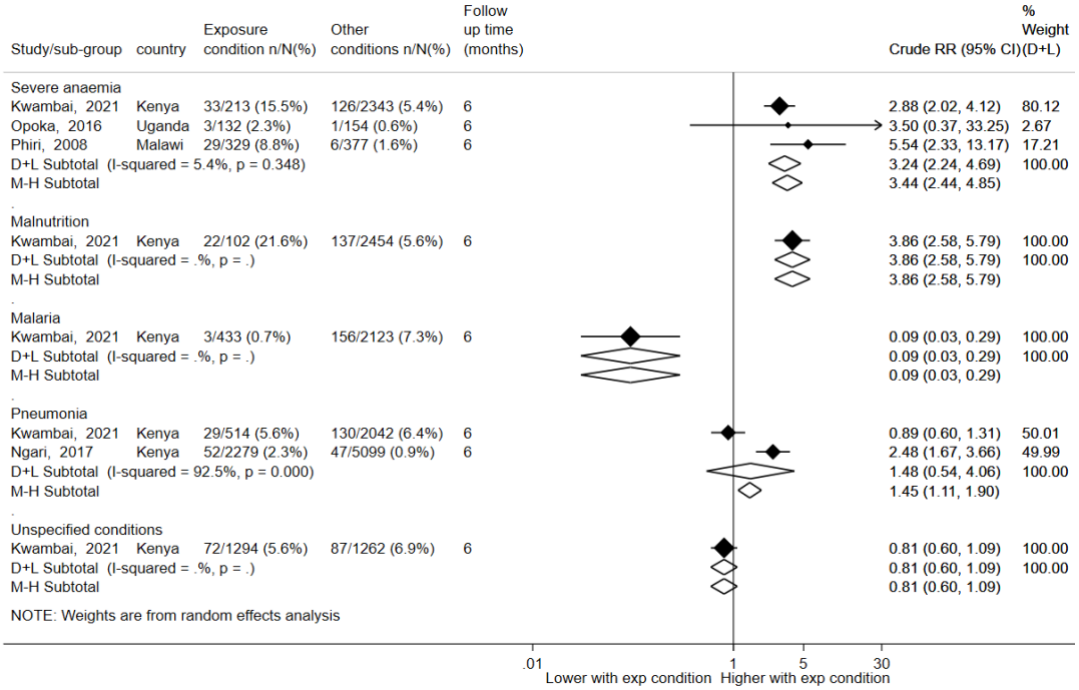
Figure S6: Other risk factors for post-discharge mortality



CI=confidence interval. HR=hazard ratio. Hb=haemoglobin. D+L=DerSimonian and Laird random effects. I-V=inverse-variance fixed-effect. HR=hazard ratio with the absence of the risk factor as the reference group.

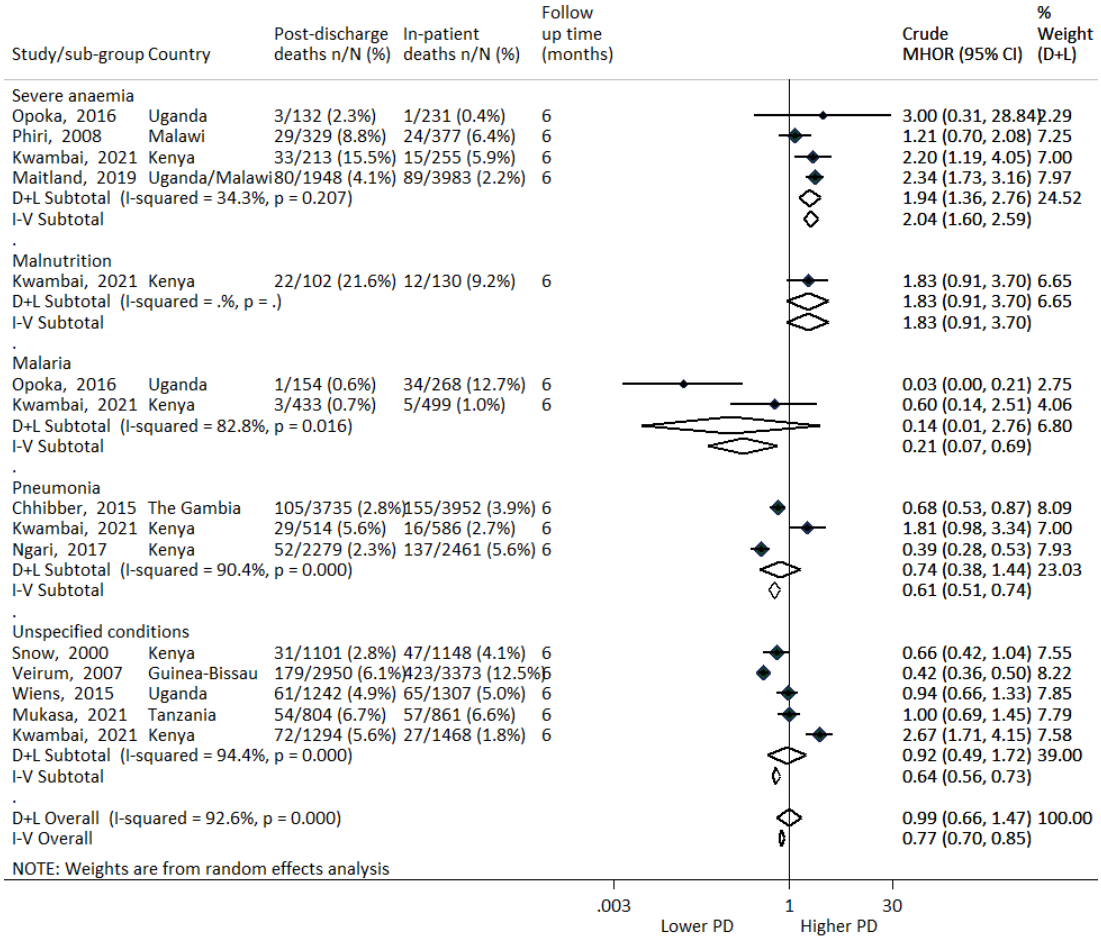
*Adjusted effect estimates were used for these data points because the crude effect estimate, or crude data (n/N) were not available

Figure S7: Sensitivity analysis restricted to studies that included at least six months follow-up for relative risk of mortality by six-month post-discharge among studies reporting results by multiple health conditions



RR=relative risk. CI=confidence interval. D+L=DerSimonian and Laird random effects. M-H=Mantel-Haenszel fixed effect. Exp=exposure group Includes only studies that reported enough detail to allow direct comparisons of the post-discharge mortality by health condition among children from the same cohort study. Diamond shapes depict the pooled effect size. The crude RR is calculated by comparing the "exposure condition" vs "other conditions". For example, in the first section under "Severe anaemia", the random effects summary crude RR of 3.24 (95% CI 2.24-4.69) represents the relative risk of post-discharge mortality comparing children who were recently admitted with severe anaemia versus all other children that were admitted for any other conditions that excluded severe anaemia ("Other conditions"), such as severe acute malnutrition, severe malaria, severe pneumonia or other unspecified conditions). Similarly, the second section under malnutrition (summary random effects RR 3.86) represents the relative risk of post-discharge mortality comparing children who were recently admitted with severe acute malnutrition versus children that were admitted for any other conditions that excluded severe acute malnutrition. In the latter case, "Other conditions" includes children with severe anaemia, severe malaria, severe pneumonia or other unspecified conditions.

Figure S8: Sensitivity analysis restricted to studies that included at least six months follow-up of in-patient vs post-discharge mortality by six months by health condition on admission



D+L=DerSimonian and Laird random effects. I-V=inverse-variance fixed-effect. MHOR=Mantel-Haenszel odds ratio. PD=post-discharge. For each study, the MHOR is obtained by comparing the number of "post-discharge deaths" vs "in-patient deaths" during the initial hospitalisation.This figure is restricted to studies that followed up participants for 6 months after discharge.
D+L=DerSimonian and Laird random effects. I-V=inverse-variance fixed-effect. MHOR=Mantel-Haenszel odds ratio. PD=post-discharge. For each study, the MHOR is obtained by comparing the number of "post-discharge deaths" vs "in-patient deaths" during the initial hospitalisation.

Supplemental tables

Table S1: Characteristics of included studies

Study	Location	Dates	Comparison groups	Age Range	Admission Health-condition	Participants assessed for*	Total Enrolled	IP Death	PD Death	Re-Admission	Loss to follow-up	FUP Time
		Randomized Controlled Trials										
Kwambai et al[1]	Kenya and Uganda	2016-18	Placebo Intervention: Dihydroartemisinin-piperaquine	<5y	Severe anaemia	1, 2	525	NR	3·1%	30·1%	6.7%	6m
Maitland et al[2]	Uganda/Malawi	2014-17	Co-trimoxazole or multivitamin multimineral or iron/folate	2m-12y	Severe anaemia	1, 2, 3, 4	1948	2·2%	4·1%	18·0%	4.2%	6m
Biai et al[3]	Guinea-Bissau	2004-06	Use of malaria treatment protocols Control ward: staff not trained Intervention: staff trained	3m-5y	Malaria	1, 2	491	9·6%	1·0%	NR	5%	28d
Phiri et al[4]	Malawi	2006-09	Placebo Intervention: artemether-lumefantrine	4m-59m	SMA	1, 2, 4	708	NR	2.3%	18·5%	4.9%	6m
Pavlinac et al[5]	Kenya	2016-2019	Placebo Intervention: Azithromyzcin	1-59m	All cause	1, 2, 3, 4	696	NR	2.7%	8.2%	NR	6m
	Cohort studies without a comparator group											
Carme et al[6]	Congo	1988-89	All enrolled	≤ 14	Cerebral malaria	2	170	15·0%	6·7%	NR	37.7%	27m
Chhibber et al[7]	The Gambia	2008-12	All enrolled	2m-59m	Pneumonia+ others	1, 2, 3, 5	3,735	3·9%	2·8%	NR	1.6%	180d

Study	Location	Dates	Comparison groups	Age Range	Admission Health-condition	Participants assessed for*	Total Enrolled	IP Death	PD Death	Re-Admission	Loss to follow-up	FUP Time
Villamor et al[8]	Tanzania	1993-97	All enrolled	6m-60m	Pneumonia	1, 2, 3, 4, 5	687	3·1%	11·7%	NR	8.7%	Mean 24.7m
Wiens et al[9]	Uganda	2012-13	All enrolled	6m-5y	All cause (Infectious)	1, 2, 3, 4, 5	1,307	5·0%	4·9%	NR	1.7%	
Hennart et al[10]	Congo	1970	All enrolled	mean 46m	PEM	3	171	NR	0·2	NR	NR	5y
Kerac et al[11]	Malawi	2006-07	All enrolled	5m-14y	PEM	1, 2, 3, 4	1,024	23·2%	24·0%	7·1%	13%	1y
Opoka et al[12]	Uganda	2016-18	All enrolled	<5 y	Severe anaemia	1, 2, 3, 4	279	NR	7·9%	45·8%	1.1%	6m
Madrid et al[13]	Mozambique	2000-2016	All enrolled	2m-15y	All cause	1, 2, 3, 4, 5	25,635	NR	3·6%	NR	NR	3m
Mukasa et al[14]	Tanzania	2003-2007	All enrolled	0-5y	All cause	-	28,910	6.6%	6.7%	NR	NR	6m
		Cohort studies with comparator groups										
Moisi et al[15]	Kenya	2003-08	Post-discharge group	<15y	All cause	2, 3, 5	14,971	NR	4·5%	8·9%	NR	12m
			Community group	<15y	NR		96,029	NA	NA	NA		
Ngari et al[16]	Kenya	2007-12	Post-discharge group	1m-59m	Severe Pneumonia	1, 2, 3, 4, 5	2,461	5·6%	3·1%	NR	1.9%	1y
			Post-discharge group	1m-59m	No Severe Pneumonia		5,270	2·4%	1·3%	NR	0.9%	
Opoka et al[17]	Uganda	2008-13	Admissions with Cerebral malaria	18m-12y	Cerebral malaria	1, 2, 3, 4	162	12·7%	0·6%	3·1%	4.9%	6m
			Admissions with SMA	18m-12y	SMA		138	0·4%	2·2%	9·4%	4.3%	
			Community (not admitted)	18m-12y	Healthy		133	NA	0·0%	0·0%	2.3%	
Veirum et al[18]	Guinea-Bissau	1991-96	PD Cohort	≤15y	All cause	1, 2, 5	2,950	12·5%	7·5%	15·9%	NR	12m
			Community cohort	≤15y	All cause		8,184	NA	*MRR	0·04	NR	
Zucker et al[19]	Kenya	1991	Exposed group	6m-5y	Severe anaemia	1, 2, 3, 4, 5	293	13·0%	18·8%	NR	4% (overall)	8w

Study	Location	Dates	Comparison groups	Age Range	Admission Health-condition	Participants assessed for*	Total Enrolled	IP Death	PD Death	Re-Admission	Loss to follow-up	FUP Time
			non-exposed group	6m-5y	Non-severe anaemia		930	8·9%	11·3%	NR		
Snow et al[20]	Kenya	1992-97	Post-discharge group	≤6y	All cause	1, 2, 5	1,148	0·0	2.39/1000 pm	347	NR	1y
			Community group	≤6y	NR		2,845	NA	1·1/1000 pm	172	NR	
Phiri et al[21]	Malawi	2002-06	Cases	6-60m	Severe anaemia	1, 2, 3, 4	377	6·4%	11·6%	17·2%	17.8%	18m
			Hospital control	6-60m	No severe anaemia		377	0·0%	2·7%	9·4%	19.0%	
			Community controls	6-60m	Healthy		380	N/A	1·3%	10·0%	15.3%	
Kwambai et al[22]	Kenya	2008-2013	Admitted with severe malaria	≤5y	Severe malaria	1, 2, 3, 4, 5	1,033	1·6%	5·7%	NR	32.8%	12m
			Admitted with severe anaemia	≤5y	Severe anaemia		651	5·5%	16·1%	NR	24.4%	
			Admitted with Pneumonia	≤5y	Pneumonia		996	2·9%	8·9%	NR	24.2	
			Admitted with SAM	≤5y	Severe acute malnutrition		271	8·5%	22·1%	NR	26.9%	
			Admitted with other health conditions	≤5y	Other health conditions		1,521	1·8%	8·2%	NR	25.2%	
Chinkhumba et al[23]	Malawi	2005-06	HIV Positive	6m-59m	SAM	1, 3, 4	79	30·4%	7·3%	NR	NR	4m
			HIV Negative	6m-59m	SAM		375	8·5%	2·0%	NR	NR	
Talbert et al[24]	Kenya	2007-2015	All enrolled	2m-59m	Acute diarrhoea	1, 2, 3, 4, 5	2,626	3·7%	2·3%	NR	NR	12m
Ngari et al[25]	Kenya	2007-2016	All enrolled	5y-12y	All enrolled	1, 2, 3, 4, 5	3,196	4·1%	3·0%	NR	2.2%	12m
Hau et al[26]	Tanzania	2014	All-enrolled	2-12y	All-cause	1, 2, 3, 4, 5	537	7·7%	12·6	NR	2.0%	12m

Study	Location	Dates	Comparison groups	Age Range	Admission Health-condition	Participants assessed for*	Total Enrolled	IP Death	PD Death	Re-Admission	Loss to follow-up	FUP Time
Bwakura-Dangarembizi et al[27]	Zimbabwe and Zambia	2016-2018	HIV Positive HIV Negative	1-59m	SAM	1, 3, 4,	750	9.7%	9.1%	NR	7.0%	12m

IP=in-patient. PD=post-discharge. FUP=follow-up. SP=sulphadoxine-pyrimethamine. IPTpd=intermittent preventive treatment post-discharge. SpO2=peripheral capillary oxygen saturation. NR=not reported. SMA=severe malarial anaemia. SAM=severe acute malnutrition. NA=not applicable. MRR= mortality rate ratio. PEM=protein-energy malnutrition. Y=years. M=months. w=weeks.

* Participants assessed for 1=Severe anaemia, 2=Severe malaria, 3=Severe acute malnutrition, 4=HIV, 5=Pneumonia

Table S2: Mean and median duration of follow-up per health condition

	Follow up times (upto 6 months)			Follow up times (upto 12 months)		
Main Health Condition	**N**	**Mean (SD)**	**Median (IQR)**	**N**	**Mean (SD)**	**Median (IQR)**
Severe anaemia	8	5.5 (1.4)	6.0 (6.0-6.0)	9	7.6 (3.6)	6.0 (6.0-12.0)
Severe malaria	4	3.8 (1.7)	3.3 (2.5-5.0)	6	9.0 (4.7)	12.0 (4.0-12.0)
Severe malnutrition	4	3.8 (2.6)	4.0 (1.5-6.0)	4	5.3 (5.0)	4.0 (1.5-9.0)
Pneumonia	4	5 (2.0)	6.0 (4.0-6.0)	3	10.0 (3.5)	12.0 (6.0-12.0)
Unspecified conditions	9	4.8 (1.6)	6.0 (3.0-6.0)	11	9.6 (4.0)	12.0 (6.0-12.0)

Table S3: Cochrane collaboration tool for quality assessment of randomised controlled trials

	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Biai et al[3]	+	+	+	+	+	+	+
Phiri et al[4]	+	+	+	+	+	+	+
Kwambai[1]	+	+	+	+	+	+	+
Maitland[2]	+	+	+*	+	+	+	+
Pavlinac[5]	+	+	+	+	+	+	+

+	Low Risk of Bias	?	Unclear Risk of Bias	-	High Risk of Bias

Risk of bias assessment for included studies based on the authors' judgements for each included trial. The scores were classified as 'low risk of bias' if all criteria were met, as 'unclear risk of bias' if insufficient information was available for at least one of the criteria in the study report, or as 'high risk of bias' if at least one of the criteria was not met'. Adapted from the Cochrane Library.

* The trials by Biai[3] and Maitland[2] et al were well designed an open-label trials

Table S4: Newcastle Ottawa scale for quality assessment of cohort studies with comparison groups

Criterion	Number of stars awarded											
	Chinkhumba et al[21]	Kwambai et al[20]	Ngari et al[14]	Opkoka et al[15]	Veirum et al[16]	Zucker et al[17]	Snow et al[18]	Moisi et al[13]	Phiri et al[19]	Talbert et al[22]	Ngari et al[23]	Bwakura-Dangarembizi et al[27]
Selection												
Representativeness of exposed cohort	1	1	1	1	1	1	1	1	1	1	1	1
selection of the non-exposed cohort	1	1	1	1	1	1	1	1	1	1	1	1
Ascertainment of exposure	1	1	1	1	1	1	1	1	1	1	1	1
Demonstration that outcome of interest was not present at the start of the study	1	1	1	1	1	1	1	1	1	1	1	1
Comparability												
Comparability of cohorts on the basis of the design or analysis	2	2	2	2	1	1	1	2	2	2	2	2
Outcome												
Assessment of outcome	1	1	1	1	1	1	1	1	1	1	1	1
Was follow up long enough for outcomes to occur?	1	1	1	1	1	1	1	1	1	1	1	1
Adequacy of follow up of cohorts	0	1	0	1	0	0	0	0	1	1	1	1
Total stars awarded out of 9	8	9	8	9	7	7	7	8	9	9	9	9
Quality Assessment	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good

The Newcastle Ottawa scale is based on a star system where one star is awarded for each item under selection and outcome categories and a maximum of two stars for comparability. A maximum of nine points is assigned for the least risk of bias in three domains: 1) selection of study groups (four points); 2) comparability of groups (two points); and 3) ascertainment of outcomes (three points) for cohort studies. The quality of studies was rated based on the Newcastle Ottawa scale of 0 to 9 as; poor quality (0 -3), fair quality (4 -6) and good quality (7 -9).

Table S5: Modified Newcastle Ottawa scale for quality assessment of cohort studies without comparison

Criterion	Summary of reviewers scores									
	Carme et al[6]	Chhibber et al[7]	Hennart et al[10]	Kerac et al[11]	Villamor et al[8]	Wiens et al[9]	Opoka et al[12]	Madrid et al[13]	Hau et al[26]	Mukasa et al[14]
Selection										
Representativeness of exposed cohort	1	1	1	1	1	1	1	1	1	1
Selection of the non-exposed cohort	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ascertainment of exposure	1	1	1	1	1	1	1	1	1	1
Demonstration that outcome of interest was not present at the start of the study	0	1	1	1	1	0	1	1	1	1
Comparability										
Comparability of cohorts on the basis of the design or analysis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outcome										
Assessment of outcome	0	1	1	1	1	1	1	1	1	1
Was follow up long enough for outcomes to occur?	1	1	1	1	1	1	1	1	1	1
Adequacy of follow up of cohorts	0	1	0	1	1	1	1	1	1	1
Total stars awarded out of 6	3	6	5	6	6	5	6	6	6	6
Quality assessment	Poor	Good	Good	Good	Good	Good	Good	Good	Good	Good

This tool was used for cohort studies without a comparison group. A single group of participants with an exposure of interest were followed up to determine the outcome. In the "selection" criteria of the Newcastle Ottawa scale, the "selection of the non-exposed cohort" and the comparability criteria were omitted. The total score is six stars, with quality assessment scored as 1-2 stars (poor quality), 3-4 (fair quality) and 5-6 (good quality).

Table S6: Comparison by health condition of the crude risks of post-discharge mortality and readmissions by six- and twelve-months post-discharge

	By 6 months			By 12 months		
	RR (95% CI, P, I^2, N)	RR (95% CI, P, I^2, N)	RR (95% CI, P, I^2, N)	RR (95% CI, P, I^2, N)	RR (95% CI, P, I^2, N)	RR (95% CI, P, I^2, N)
Mortality	Versus any other health condition	Versus any other health condition, excluding severe anaemia	Versus any other health condition, excluding severe malnutrition	Versus any other health conditions	Versus any other health condition, excluding severe anaemia	Versus any other health condition, excluding severe malnutrition
Severe anaemia	2·69 (1·5961-4·53), P<0·0001, 69·2%, 4	NA	2·30 (1·11-4·78), P<0·025, 88·2%, 2	2·39 (1·51-3·80), P<0·0001, 69·0%, 4	NA	Insufficient data
Severe malnutrition	3·12 (2·07-4·68), P<0·0001, 54·7%, 2	3·26 (1·62-6·56), P=0·001, 83·0%, 2	NA	2·70 (2·07-3·52), P<0·0001, 0·0%, 2	3·26 (2·47-4·30), P<0·0001, 0·0%, 2	NA
Severe pneumonia	1·09 (0·44-2·71), P=0·846, 88·7%, 3	0·84 (0·41-1·74), P=0·643, 45·0%, 2	0·88 (0·50-1·53), P=0·641, 25·2%, 2	1·62 (0·71-3·67), P=0·249, 92·2%, 2	1·44 (0·79-2·62), P=0·237, 83·0%, 3	1·12 (0·83-1·50), P=0·454, 0·0%, 2
Not defined	1·02 (0·63-1·670), P=0·929, 75·5%, 2	1·15 (0·90-1·47), P=0·274, 0·0%, 2	1·28 (1·01-1·62), P=0·040, 0·0%, 2	0·98 (0·56-1·72), P=0·949, 83·3%, 2	0·90 (0·72-1·12), P=0·336, 0·0%, 2	1·06 (0·76-1·48), P=0·736, 53·3%, 2
Severe malaria	0·39 (0·14-1·05), P=0·061, 87·8%, 3	0·33 (0·03-3·41), P=0·351, 93·3%, 2	0·32 (0·03-3·44), P=0·348, 93·5, 2	0·51 (0·25-1·04), P=0·066, 83·0%, 3	0·57 (0·18-1·80), P=0·336, 90·1%, 2	0·55 (0·17-1·82), P=0·328, 90·8%, 2
Readmissions						
Severe anaemia	3·05 (1·12-8·35), P<0·0001, 0·0%, 1	NA	Insufficient data	Insufficient data	N/A	Insufficient data

RR=relative risk. CI=confidence interval. The effect estimates shown in the second column from the left is the same as shown in Figure *3* (given for illustration purposes only)

Table S7: Risk factors for post discharge mortality

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
Moisi[15]	Age 1–5 months (ref: <1 month)	HR	1·34 (0·93-1·92)	Yes
	Age 6–11 months (ref: <1 month)	HR	0·82 (0·57-1·18)	Yes
	Age 2–5 years (ref: <1 month)	HR	0·57 (0·36-0·90)	Yes
	Weigh for age z-score < −3	HR	3·42 (2·50-4·68)	Yes
	Weigh for age z-score < −4	HR	6·53 (4·85-8·80)	Yes
	Parasitaemia (ref: no parasitaemia)	HR	0·45 (0·29-0·71)	Yes
	Hypoxia (ref: no hypoxia)	HR	2·3 (1·64-3·23)	Yes
	Bacteraemia (ref: no bacteraemia)	HR	1·77 (1·15-2·74)	Yes
	Jaundice (ref: no jaundice)	HR	1·77 (1·08-2·91)	Yes
	Hepatomegaly (ref: no hepatomegaly)	HR	2·34 (1·60-3·42)	Yes
	Hospitalization > 13 d (ref: <13 days)	HR	1·83 (1·33-2·52)	Yes
	1 prior discharge (within a 1 year of index discharge) (ref: no prior discharge)	HR	2·83 (2·04-3·92)	Yes
	2 prior discharges (within a 1 year of index discharge) (ref: no prior discharge)	HR	7·06 (4·09-12·21)	Yes
	≥ 3 prior discharges (within a 1 year of index discharge) (ref: no prior discharge)	HR	23·55 (10·70-51·84)	Yes
	Mild pneumonia (ref: no pneumonia)	HR	2·30 (1·00-5·28)	Yes
	Severe pneumonia (ref: no pneumonia)	HR	1·37 (1·05-1·79)	Yes
	Very severe pneumonia (ref: no pneumonia)	HR	4·09 (2·25-7·46)	Yes
	Severe malnutrition (ref: no malnutrition)	HR	4·37 (2·73-7·01)	Yes
	Meningitis (ref: no meningitis)	HR	2.29 (1.57-3.32)	Yes
	Sick young infant	HR	2·67 (1·98-3·58)	Yes
Wiens[9]	Male sex (ref: female)	OR	0·90 (0·54-1·51)	No
	Age (months) (per unit increase)	OR	0·97 (0·97-0·97)	No
	MUAC (per mm increase)	OR	0·97 (0·96-0·98)	No
	Weight for age z-score (per unit increase)	OR	0·66 (0·57-0·76)	No

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Weight for length/height z-score (per unit increase)	OR	0·81 (0·72-0·91)	No
	Length/height for age z-score (per unit increase)	OR	0·79 (0·7-0·89)	No
	Heart rate for age z-score	OR	0·86 (0·74-0·99)	No
	Heart rate (raw)	OR	1·00 (0·99-1·01)	No
	Respiratory rate for age z-score	OR	0·99 (0·92-1·06)	No
	Respiratory rate (raw)	OR	1·01 (1·00-1·03)	No
	Systolic blood pressure z-score	OR	0·94 (0·79-1·12)	No
	Systolic blood pressure (raw)	OR	0·98 (0·96-1·00)	No
	Diastolic blood pressure (raw)	OR	0·99 (0·97-1·01)	No
	Temperature (transformed)	OR	1·02 (0·90-1·16)	No
	Temperature (raw)	OR	0·76 (0·62-0·93)	No
	SpO2 (raw) (per 1% increase)	OR	0·94 (0·92-0·96)	No
	SpO2 (transformed) (per 1% increase)	OR	1·04 (1·02-1·05)	No
	HIV positive (ref: negative)	OR	5·21 (2·55-10·65)	No
	Hb (g/dL)	OR	0·95 (0·87-1·03)	No
	Blantyre Coma Scale <5 (ref: 5)	OR	2·40 (1·27-4·57)	No
	Positive blood smear (vs negative)	OR	0·33 (0·16-0·68)	No
	Illness >7 days prior to admission	OR	0·50 (0·30-0·83)	No
	Time since last hospitalisation (Ordered as <7 days, 7 to 30 days, 30 days to 1 year, >1 year and never (analysed as continuous and coded and 1–5, respectively)	OR	0·75 (0·62-0·90)	No
	Sibling deaths	OR	1·54 (0·89-2·65)	No
	Number of children in family	OR	1·02 (0·92-1·13)	No
	Boil all drinking water	OR	0·82 (0·47-1·42	No
	Maternal age (years)	OR	1·00 (0·97-1·04)	No
	Mother HIV positive (ref: negative)	OR	1·79 (0·87-3·67)	No

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Mother HIV status unknown (ref: negative))	OR	1·27 (0·64-2·52)	No
	Maternal education (Primary) (ref: <primary 3)	OR	1·18 (0·62-2·23)	No
	Maternal education (Some) (ref: <primary 3)	OR	0·72 (0·31-1·70)	No
	Maternal education (Postsecondary) (ref: <primary 3)	OR	1·18 (0·41-3·36)	No
	Bed net use (Sometimes) (ref: never)	OR	1·00 (0·48-2·09)	No
	Bed net use (always) (ref: never)	OR	0·85 (0·46-1·58)	No
	Distance from hospital (30–60 minutes) (ref: <30 min)	OR	0·71 (0·31-1·64)	No
	Distance from hospital (>60 minutes) (ref: <30 min)	OR	1·30 (0·70-2·41)	No
Phiri[21]	Unit increase in age (months)	HR	0·92 (0·87-0·97)	Yes
	Rural residency (ref: urban)	HR	1·63 (0·63-4·20)	Yes
	Sex (Male)	HR	1·54 (0·68-3·52)	Yes
	Maternal education (Some) (ref: none)	HR	1·63 (0·72-3·70)	No
	Parents unemployed (ref: employed)	HR	4·15 (1·61-10·74)	Yes
	Weight-for-height (WHZ) <-2 Z-score (≥-2 Z-score WHZ)	HR	0·74 (0·31-1·80)	No
	Height-for-age (HAZ) <-2 Z-score (≥-2 Z-score HAZ)	HR	0·61 (0·30-1·22)	No
	Splenomegaly (ref: no splenomegaly)	HR	0·36 (0·16-0·80)	Yes
	Iron deficiency ≥5.6 sTfR/Log ferritin (ref: <5.6 sTfR/Log ferritin)	HR	0·91 (0·41-2·03)	No
	Any malaria parasite/µL blood (ref: no parasitaemia)	HR	1·25 (0·67-2·34)	No
	HIV Positive (ref: HIV negative)	HR	10·49 (4·05-27·20)	Yes
	Bacteraemia (ref: no bacteraemia)	HR	2·17 (0·84-5·64)	Yes
Ngari[16]	Age 12–23 months (ref: ≥24 months)	HR	1·02 (0·1-9·6)	Yes
	Age 6–11 months (ref: ≥24 months)	HR	5·8 (0·8-40·5)	Yes
	Age <6 months (ref: ≥24 months)	HR	4·8 (0·7-34·1)	Yes
	Sex (male)	HR	1·45 (0·75-2·83)	Yes
	Reported preterm/low birthweight (LBW) (ref: no preterm/LBW)	HR	0·7 (0·2-2·8)	Yes

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Residence distance (from study site per KM)	HR	1·0 (0·9-1·1)	Yes
	Duration of hospitalisation per day	HR	1·1 (1·0-1·2)	Yes
	Hypoxia (SaPO2 <90%) (ref: SaPO2 >90%)	HR	1·9 (0·7-5·4)	Yes
	Capillary refill >2 seconds (ref: <2seconds)	HR	2·4 (0·5-12·1)	Yes
	Impaired consciousness (ref: normal consciousness)	HR	1·1 (0·2-7·8)	Yes
	Wheezing (ref: no wheezing)	HR	0·5 (0·1-2·4)	Yes
	Cough for >14 days	HR	0·2 (0·1-5·5)	Yes
	Jaundice (ref: no jaundice)	HR	12·5 (1·1-13·7)	Yes
	Severe anaemia (Hb <5g/dL) (ref: Hb≥5)	HR	0·8 (0·1-7·5)	Yes
	Axillary temperature <36°C (ref: axillary temperature 36 to 39oc)	HR	0·3 (0·1-2·8)	Yes
	Axillary temperature >39°C (ref: axillary temperature 36 to 39oc)	HR	1·1 (0·4-3·0)	Yes
	HIV antibody test positive (ref: HIV negative)	HR	6·5 (2·3-18·4)	Yes
	HIV test not performed (ref: HIV negative)	HR	0·4 (0·1-3·6)	Yes
	Respiratory Syncytial Virus test positive (ref: RSV test negative)	HR	0·3 (0·1-1·2)	Yes
	Respiratory Syncytial Virus test not performed (ref: RSV test negative)	HR	2·7 (1·2-6·3)	Yes
	Malaria slide positive (ref: negative)	HR	0·5 (0·1-5·2)	Yes
	Bacteraemia (ref: no bacteraemia)	HR	0·8 (0·1-5·2)	Yes
	MUAC per cm increase	HR	0·6 (0·5-0·8)	Yes
	Year of admission 2008 (ref: Year of admission 2007)	HR	0·9 (0·3-3·1)	Yes
	Year of admission 2009 (ref: Year of admission 2007)	HR	0·5 (0·1-2·1)	Yes
	Year of admission 2010 (ref: Year of admission 2007)	HR	0·7 (0·2-2·5)	Yes
	Year of admission 2011 (ref: Year of admission 2007)	HR	1·7 (0·5-5·3)	Yes
	Year of admission 2012 (ref: Year of admission 2007)	HR	1·8 (0·2-15·7)	Yes
Villamor[8]	HIV Positive (ref: HIV negative)	HR	3·92 (2·34-6·55)	Yes
	Sex Male	HR	0·98 (0·65-1·48)	No

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Age 6–11 months (ref: ≥24 months)	HR	3·70 (1·72-7·95)	Yes
	Age 12–23 months (ref: ≥24 months)	HR	3·14 (1·44-6·88)	Yes
	Height-for-age <-2 Z-score (ref: HAZ>-2 Z-score)	HR	2·12 (1·31-3·42)	Yes
	Low MUAC at baseline (MUAC <25th percentile of the population age-specific distribution) (per cm increase)	HR	1·88 (1·16-3·03)	Yes
	Hb ≤7.00 g/dL (ref: Hb >10.00g/dL)	HR	2·55 (1·13-5·77)	Yes
	Hb 7.01–8.50 g/dL (ref: Hb >10.00g/dL)	HR	2·81 (1·24-6·37)	Yes
	Hb 8.51–10.00 g/dL (ref: Hb >10.00g/dL)	HR	1·76 (0·75-4·10)	Yes
	Severe pneumonia on admission (ref: no pneumonia on admission)	HR	2·47 (1·59-3·85)	Yes
	Maternal education (Elementary) (ref: None/illiterate)	HR	0·84 (0·48-1·49)	No
	Maternal education (Secondary or higher) (ref: None/illiterate)	HR	0·27 (0·06-1·17)	No
	Tap in compound (ref: tap in house)	HR	1·40 (0·60-3·29)	Yes
	Tap outside compound (ref: tap in the house)	HR	2·27 (1·02-5·03)	Yes
	Public well (ref: tap in the house)	HR	2·92 (1·03-8·30)	Yes
	Mother works outside home-yes (ref: no)	HR	0·61 (0·36-1·03)	No
	Mother lives with a partner (ref: mother lives without a partner)	HR	1·60 (1·00-2·57)	No
	No household amenity (ref: 1 household amenity) (from a list of five items: car, refrigerator, radio, bicycle, and television)	HR	1·58 (0·92-2·69)	No
	2≤ household amenities (ref: 1 household amenity)	HR	0·95 (0·56-1·60)	No
Kerac[11]	Sex (Male)	HR	0·89 (0·73-1·08)	Yes
	Age >=60 months (ref: age 48 to 60 months)	HR	1·22 (0·63-2·36)	Yes
	Age 36 to 48 months (ref: age 48 to 60 months)	HR	1·66 (0·84-3·29)	Yes
	Age 24 to 36 months (ref: age 48 to 60 months)	HR	1·38 (0·76-2·49)	Yes
	Age 12 to 24 months (ref: age 48 to 60 months)	HR	1·57 (0·89-2·78)	Yes
	Age <12 months (ref: age 48 to 60 months)	HR	2·49 (1·38-4·51)	Yes

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Oedema (ref: no oedema)	HR	0·58 (0·47-0·72)	Yes
	MUAC per cm increase	HR	0·80 (0·74-0·86)	Yes
	weight-for-height (per 1-unit z-score increase)	HR	0·75 (0·68-0·83)	Yes
	Weight for age (per 1-unit z-score increase)	HR	0·73 (0·66-0·81)	Yes
	height for age z-score (per 1-unit z-score increase)	HR	0·92 (0·86-0·99)	Yes
	HIV Positive (ref: HIV negative)	HR	4·03 (3·08-5·25)	Yes
	HIV status unknown (ref: HIV negative)	HR	16·9 (12·1-23·7)	Yes
Chhibber[7]	Sepsis with clinically severe malnutrition (ref: pneumonia without clinically severe malnutrition)	HR	18·4 (11·3-30·0)	Yes
	Meningitis with clinically severe malnutrition (ref: pneumonia without clinically severe malnutrition)	HR	13·7 (4·2-44·7)	Yes
	Pneumonia with clinically severe malnutrition (ref: pneumonia without clinically severe malnutrition)	HR	8·1 (4·4-14·8)	Yes
	Meningitis without clinically severe malnutrition (ref: pneumonia without clinically severe malnutrition)	HR	2·6 (1·2-5·5)	Yes
	Sepsis without clinically severe malnutrition (ref: pneumonia without clinically severe malnutrition)	HR	2·2 (1·1-4·3)	Yes
	Age in months (mean [SD])	HR	1·00 (0·98-1·03)	Yes
	Neck stiffness (ref: no neck stiffness)	HR	10·4 (3·1-34·8)	Yes
	Non-medical discharge (i.e. discharge against medical advice) (ref: medical discharge)	HR	4·68 (2·01-10·85)	Yes
	Axillary temperature (°C) (mean [SD])	HR	0·71 (0·58-0·87)	Yes
	Oxygen saturation (% increase)	HR	0·96 (0·93-0·99)	Yes
	Hb in g/dL (mean [SD])	HR	0·82 (0·73-0·91)	Yes
	MUAC 11.5–13.0 cm (ref: MUAC>13cm)	HR	7·19 (3·04-17·01)	Yes
	MUAC 10.5–11.4 cm (ref: MUAC>13cm)	HR	24·2 (9·4-61.9)	Yes
	MUAC <10.5 cm (ref: MUAC>13cm)	HR	43·7 (17·7-108)	Yes

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
Veirum[18]	Discharge age 5 years+ (ref: 1-12 months)	RR	0·15 (0·05-0·30)	Yes
	Discharge age 4 years (ref: 1-12 months)	RR	0·23 (0·09-0·48)	Yes
	Discharge age 3 years (ref: 1-12 months)	RR	0·14 (0·04-0·39)	Yes
	Discharge age 2 years (ref: 1-12 months)	RR	0·52 (0·25-0·76)	Yes
	Discharge age 1 year (ref: 1-12 months)	RR	0·82 (0·67-1·41)	Yes
	Neonatal (ref: 1-12 months)	RR	0·69 (0·21-1·77)	Yes
	Mothers' education (ref: no education)	RR	0·74 (0·56-1·14)	Yes
	Non-medical discharge (against medical advice) (ref: medical discharge)	RR	8·51 (5·32-13·59)	Yes
	Other (ref: malaria)	RR	1·65 (1·02-2·92)	Yes
	Anaemia (ref: malaria)	RR	1·97 (0·97-4·00)	Yes
	Diarrhoea (ref: malaria)	RR	1·82 (0·83-2·35)	Yes
	Bronchopneumonia (ref: malaria)	RR	0·98 (0·66-1·74)	Yes
	Measles (ref: malaria)	RR	0·77 (0·43-2·22)	Yes
Hue et al[26]	Age 5 – 12 years (ref: <5 years)	HR	1·75 (1·15 – 2·68)	No
	Age 5-12 years (ref: <5 years)	HR	1·01 (1·00-1·01)	Yes
	Pit latrine at home (ref: none)	HR	1·58 (1·00-2·50)	No
	Sex (ref: female)	HR	0·84 (0·55-1·28)	No
	Lake or pond as a water source (ref: no)	HR	1·10 (0·71-1·69)	No
	HIV Status (HIV negative)	HR	1·38 (0·60-3·16)	No
	Decreased urine output (ref: no)	HR	4·95 (2·83-8·66)	No
	Diarrhoea (ref: no diarrhoea)	HR	0·11 (0·39-1·11)	No
	Fever (ref: none)	HR	0·86 (0·54-1·36)	No
	Vomiting (ref: none)	HR	1·02 (0·63-1·63)	No
	Oxygen saturation: per % increase	HR	0·93 (0·91-0·95)	No
	Oxygen saturation: per % increase	HR	0·93 (0·89-0·98)	Yes

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Glasgow coma scale 13-14 (ref: <13)	HR	0·66 (0·60-0·73)	No
	Bilateral lower extremity oedema (ref: none)	HR	2·31 (1·40-3·81)	No
	Respiratory Rate-bpm (per unit increase) 2-5 years	HR	1·04 (1·02-1·06)	No
	Respiratory Rate-bpm (per unit increase) 6-12 years	HR	1·02 (1·00-1·04)	No
	Diastolic blood pressure, mean mm Hg (per unit increase) 2-5 years	HR	0·99 (0·96-1·02)	No
	Diastolic blood pressure, mean mm Hg (per unit increase) 6-12 years	HR	0·94 (0·91-0·98)	No
	Heart rate, beats per minute, mean (SD) (per unit increase) 2-5 years	HR	1·00 (0·99-1·02)	No
	Heart rate, beats per minute, mean (SD) (per unit increase) 6-12 years	HR	1·01 (0·99-1·02)	No
	Systolic blood pressure, mean mm Hg (per unit increase) 2-5 years	HR	1·00 (0·98-1·02)	No
	Systolic blood pressure, mean mm Hg (per unit increase) 6-12 years	HR	0·97 (0·95-1·00)	No
	Severe Malnutrition (ref: normal)	HR	1·49 (0·83-2·70)	No
	Moderate Malnutrition (ref: normal)	HR	1·07 (0·57-1·98)	No
	Mild Malnutrition (ref: normal)	HR	0·99 (0·55-1·77)	No
	Temperature, Celsius, mean (SD)	HR	1·05 (0·84-1·30)	No
	Hb level, g/dL, mean (SD) (per unit increase)	HR	0·82 (0·75-0·88)	No
	Hb level, g/dL, mean (SD) (per unit increase)	HR	0·79 (0·70-0·88)	Yes
	Proteinuria by urinalysis (ref: none)	HR	2·38 (1·51-3·74)	No
	Proteinuria by urinalysis (ref: none)	HR	2·13 (1·12-4·05)	Yes
	Haematuria by urinalysis (ref: none)	HR	2·81 (1·35-5·81)	No
	Glomerular filtration rate < 60 ml/min/1.73m2 (ref: no)	HR	1·91 (1·21-3·02)	No
	Random blood glucose, mg/dL, mean (SD) (per unit increase)	HR	0·98 (0·90-1·05)	No
	Cancer (ref: respiratory infections & malaria)	HR	11·79 (4·95-28·03)	No
	Heart disease (ref: respiratory infections & malaria)	HR	7·11 (2·89-17·51)	No
	Sickle cell disease (ref: respiratory infections & malaria	HR	3·32 (1·44-7·68)	No
	Neurologic diseases (ref: respiratory infections & malaria)	HR	3·51 (1·35-9·11)	No

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Septic shock (ref: respiratory infections & malaria)	HR	4·64 (1·42-15·08)	No
	Severe malnutrition (ref: respiratory infections & malaria)	HR	3·19 (1·18-8·57)	No
	Anaemia (ref: respiratory infections & malaria)	HR	2·03 (0·75-5·46)	No
	Diarrheal diseases (ref: respiratory infections & malaria)	HR	1·94 (0·75-5·04)	No
	Diarrheal diseases (ref: respiratory infections & malaria)	HR	0·49 (0·20-1·17)	Yes
	Other (ref: respiratory infections & malaria)	HR	1·96 (0·73-5·27)	No
	Decreased urine output (ref: no)	HR	4·95 (2·83-8·66)	No
	Diarrhoea (ref: no diarrhoea)	HR	0·114 (0·39-1·11)	No
	Fever (ref: none)	HR	0·86 (0·54-1·36)	No
	Vomiting (ref: none)	HR	1·02 (0·63-1·63)	No
Madrid et al[13]	Age 4 to < 1 year (ref: <3 months)	HR	0·86 (0·70 –1·06)	No
	Age 1 to 5 years (ref: <3 months)	HR	0·50 (0·41-0·60)	No
	Age >5 years (ref: <3 months)	HR	0·35 (0·26-0·46)	No
	Female sex	HR	1·01 (0·89-1·15)	No
	Rainy season	HR	1·16 (1·02-1·33)	No
	Weight for height *z* score (mean ± SD)	HR	0·63 (0·57-0·69)	No
	WHZ *z* score, SD (ref:>-1): >−2 to <−1	HR	1·34 (0·88-2·04)	No
	WHZ *z* score, SD (ref:>-1): >−3 to <−2	HR	2·42 (1·58-3·71)	No
	WHZ *z* score, SD (ref:>-1): >−3	HR	5·94 (4·12-8·57)	No
	History of fever	HR	0·54 (0·45-0·64)	No
	History of cough	HR	1·78 (1·53-2·06)	No
	History of diarrhoea	HR	2·36 (2·06-2·69)	No
	History of vomiting	HR	1·32 (1·15-1·52)	No
	History of difficulty in breathing	HR	1·81 (1·58-2·08)	No
	History of anorexia	HR	1·79 (1·46-2·20)	No

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	History of blood in urine	HR	1·43 (0·59-3·44)	No
	History of seizures	HR	0·37 (0·27-0·51)	No
	Axillary temperature <35.5 (ref: 35.5^{0}C-37.4^{0}C)	HR	1·31 (0·90-1·89)	No
	Axillary temperature >37.5 (ref: 35.5^{0}C-37.4^{0}C)	HR	0·67 (0·59-0·77)	No
	Bradycardia	HR	1·10 (0·87-1·40)	No
	Tachycardia	HR	1·05 (0·90-1·21)	No
	Increased respiratory rate	HR	1·37 (1·20-1·57)	No
	Dehydration	HR	2·04 (1·77-2·37)	No
	Pallor	HR	0·90 (0·75-1·07)	No
	Jaundice	HR	0·88 (0·33-1·32)	No
	Oedema (any location)	HR	2·96 (2·46-3·57)	No
	Skin flaking off	HR	2·90 (2·15-3·90)	No
	Depigmented or reddish hair	HR	5·30 (4·55-6·18)	No
	Oral candidiasis	HR	7·44 (6·08-9·09)	No
	Swollen lymph nodes	HR	4·33 (3·56-5·25)	No
	Conjunctivitis	HR	1·62 (1·08-2·43)	No
	Ear discharge	HR	2·59 (1·98-3·38)	No
	Lower chest wall indrawing	HR	1·73 (1·51-1·99)	No
	Nasal flaring	HR	1·48 (1·27-1·73)	No
	Pathologic breathing pattern	HR	1·50 (1·14-1·97)	No
	Auscultatory crackles	HR	2·02 (1·77-2·31)	No
	Wheeze and/or rhonchus	HR	1·15 (0·96-1·39)	No
	Hepatomegaly	HR	1·57 (1·14-2·18)	No
	Splenomegaly	HR	0·69 (0·58-0·82)	No
	Blantyre coma scale (3-4): (ref:5)	HR	1·26 (0·91-1·73)	No

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Blantyre coma scale (≤2): (ref:5)	HR	1·57 (1·03-2·41)	No
	Malaria positive test: (ref: negative test)	HR	0·26 (0·22-0·31)	No
	Malaria test not done: (ref: negative test)	HR	0·61 (0·51-0·74)	No
	Hypoglycaemia (<2.5): (ref: 2.5-11.0)	HR	0·92 (0·73-1·15)	No
	Hyperglycaemia (>11.0): (ref: 2.5-11.0)	HR	0·78 (0·60-1·03)	No
	Blood culture result positive: (ref: negative)	HR	3·32 (2·77-3·98)	No
	Anaemia mild to moderate: (ref: no anaemia)	HR	1·00 (0·87-1·15)	No
	Anaemia severe: (ref: no anaemia)	HR	1·04 (0·84-1·28)	No
	HIV status negative (ref: test not done)	HR	0·55 (0·37-0·82)	No
	HIV status positive (ref: test not done)	HR	4·97 (3·59-6·88)	No
	Absconded from hospital	HR	8·18 (6·87-9·74)	No
	Transferred to another hospital	HR	6·30 (5·12-7·75)	No
Talbert et al[24]	Age (months)	HR	1·00 (0·97-1·02)	No
	Sex (female): (ref: male)	HR	1·12 (0·64-1·96)	No
	Prior hospital admission: (ref: no prior hospitalization)	HR	4·71 (2·66-8·32)	No
	Prior hospital admission: (ref: no prior hospitalisation)	HR	3·11 (1·57-6·17)	Yes
	Persistent diarrhoea	HR	3·51 (1·11-11·13)	No
	Bloody diarrhoea	HR	0·90 (0·12-6·46)	No
	Some dehydration: (ref: no dehydration)	HR	0.90 (0.40-2.04)	No
	Severe dehydration: (ref: no dehydration)	HR	1·92 (1·02-3·61)	No
	Tachypnoea: (ref: no tachypnoea)	HR	1·50 (0·83-2·68)	No
	Tachycardia: ref: no tachycardia)	HR	0·95 (0·53-1·68)	No
	Lower chest wall indrawing: (ref: no lower chest wall indrawing)	HR	2·90 (1·59-5·26)	No
	Lower chest wall indrawing: (ref: no lower chest wall indrawing)	HR	2·00 (1·03-3·79)	Yes
	Hypoxia (SaO2 < 90%): (ref: SaO2 ≥90%)	HR	2·03 (0·49-8·34)	No

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Capillary refill > 2 s: (ref: Capillary refill ≤2 seconds)	HR	3·16 (1·35-7·43)	No
	Temperature gradient: (ref: no temperature gradient)	HR	1·85 (0·83-4·12)	No
	Impaired consciousness: (ref: normal conscious level)	HR	2·75 (1·17-6·45)	No
	HIV antibody positive: (ref: HIV antibody negative)	HR	13·76 (7·60-24·91)	No
	HIV antibody positive: (ref: HIV antibody negative)	HR	5·02 (2·31-10·92)	Yes
	Bacteraemia (ref: no bacteraemia)	HR	5·41 (2·27-12·89)	No
	Bacteraemia: (ref: no bacteraemia)	HR	3·69 (1·64-10·14)	Yes
	Malaria slide positive: (ref: malaria slide negative)	HR	0·48 (0·47-4·93)	No
	Severe anaemia (Hb < 5 g/dL)	HR	4·20 (1·78-9·90)	No
	MUAC per centimetre	HR	0·55 (0·47-0·64)	No
	MUAC per centimetre	HR	0·67 (0·56-0·81)	Yes
	Height-for-age z score	HR	0·62 (0·52-0·73)	No
Ngari 2020[25]	Weak pulse: (ref: normal pulse)	HR	3·54 (1·64-7·64)	Yes
	HIV positive: (ref: HIV negative)	HR	3·06 (1·69-5·54)	Yes
	Malaria positive: (ref: malaria negative)	HR	0·43 (0·20-0·93)	Yes
	Moderate anaemia: (ref: no anaemia)	HR	1·38 (0·73-2·61)	Yes
	Severe anaemia: (ref: no anaemia)	HR	2·34 (1·18-4·63)	Yes
	MUAC-for-age Z score -3 to -2: (ref: ≥-2)	HR	1·66 (0·95-2·91)	Yes
	MUAC-for-age Z score <-3: (ref: ≥-2)	HR	3·74 (2·24-6·25)	Yes
Bwakura-Dangarembizi 2021[27]	Sex (male): (ref: female)	HR	1·15 (0·67-1·97)	Yes
	HIV Positive: (ref: Negative)	HR	3·83 (2·15-6·82)	Yes
	Nonoedematous SAM: (ref: oedematous SAM)	HR	2·23 (1·24-4·01)	Yes
	SAM at discharge: (ref: no SAM at discharge)	HR	2·28 (1·22-4·25)	Yes

Author	Risk factor	Effect Measure	EM (95% CI)	Adjusted
	Cerebral palsy: (ref: no Cerebral palsy)	HR	5·60 (2·72-11·50)	Yes
Mukasa 2021[14]	Less poor households: (ref: Least Poor households)	HR	0.55 (0·22-1·37)	No
	Poor households: (ref: Least Poor households)	HR	1·04 (0·48-2·24)	No
	Very poor households: (ref: Least Poor households)	HR	1·13 (0·52-2·44)	No
	Poorest households: (ref: Least Poor households)	HR	0·88 (0·34-2·29)	No
	Anemia: (ref: Malaria)	HR	0·89 (0·37-2·22)	No
	Pneumonia: (ref: Malaria)	HR	1·20 (0·41-3·43)	No
	Diarrhoea: (ref: Malaria)	HR	0·57 (0·16-2·09)	No
	Others: (ref: Malaria)	HR	0·65 (0·31-1·34)	No
	Proximity to hospital, 25‑ < 50 Km: (ref: <25Km)	HR	0·92 (0·43-2·01)	No
	Proximity to hospital, 50‑ < 75 Km: (ref: <25Km)	HR	1·48 (0·68-3·23)	No
	Proximity to hospital, ≥ 75 Km: (ref: <25Km)	HR	3·55 (1·77-7·11)	No

HR=hazard ratio. MUAC=mid-upper arm circumference. SD=standard deviation. Hb=haemoglobin. HIV=human immunodeficiency virus. g/dL=grams per decilitre. mg/dl=milligrams per decilitre. SaO_2<90%=arterial blood oxygen saturation less than 90%. SpO_2, oxygen saturation as detected by the pulse oximeter

Table S8: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review=meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2 and 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving a rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2 and 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in a systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, S3
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, the difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of the risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 and, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table S1
Risk of bias within studies	19	Present data on the risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S2, Table S3 Table S4 and Table S5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2, Figure 3, Figure 4, Figure S1, Figure S2, Figure S3, Figure S4, Figure S5 , Figure S6, Figure S7, Figure S8

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2, Figure 3, Figure 4, Figure S1, Figure S2, Figure S3, Figure S4, Figure S5 , Figure S6, Figure S7, Figure S8
Risk of bias across studies	22	Present results of any assessment of the risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers).	8 to 10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., the supply of data); the role of funders for the systematic review.	2 and 6

Supplemental references

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