BMJ Open

Post-Discharge Mortality in Children with Acute Infectious Diseases: Derivation of Post-Discharge Mortality Prediction Models

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-009449
Article Type:	Research
Date Submitted by the Author:	21-Jul-2015
Complete List of Authors:	Wiens, Matthew; University of British Columbia, School of Population and Public Health Kumbakumba, Elias; Mbarara University of Science and Technology, Department of Pediatrics Larson, Charles P ; University of British Columbia, Department of Pediatrics/Centre for International Child Health, BC Children's Hospital Ansermino, Mark; University of British Columbia, Department of Pediatric Anesthesia Singer, Joel; University of British Columbia, School of Population and Public Health Kissoon, Niranjan; University of British Columbia, Department of Pediatrics Wong, Hubert; University of British Columbia, School of Population and Public Health Ndamira, Andrew; Mbarara University of Science and Technology, Department of Pediatarics Kabakyenga, Jerome; Mbarara University of Science and Technology, Maternal, Newborn and Child health Institute Kiwanuka, Julius; Mbarara University of Science and Technology, Department of Pediatarics Zhou, Guohai; University of British Columbia, Department of Statistics
Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Infectious diseases, Paediatrics
Keywords:	PAEDIATRICS, EPIDEMIOLOGY, Paediatric infectious disease & immunisation < PAEDIATRICS

Post-Discharge Mortality in Children with Acute Infectious Diseases: Derivation of Post-Discharge Mortality Prediction Models

MO Wiens[1], E Kumbakumba[2], CP Larson[3], JM Ansermino[4], J Singer[1,6], N Kissoon[5], H Wong[1], A Ndamira[2], J Kabakyenga[7], J Kiwanuka[2], G Zhou[8]

1. School of Population and Public Health, University of British Columbia, Vancouver, Canada
2. Department of Pediatrics, Mbarara University of Science and Technology, Mbarara, Uganda
3. Center for International Child Health, BC Children's Hospital, Child and Family Research Institute, Vancouver Canada
4. Department of Pediatric Anesthesiology, BC Children's Hospital and University of British Columbia, Vancouver, Canada
5. Department of Pediatrics, BC Children's Hospital and University of British Columbia, Vancouver, Canada
6. Canadian HIV Trials Network, St. Paul's Hospital and University of British Columbia, Vancouver, Canada
7. Maternal, Newborn and Child Health Institute, Mbarara University of Science and Technology, Mbarara, Uganda
8. Department of statistics, University of British Columbia, Vancouver, Canada

Word count: 3344

Correspondence to:

Matthew Wiens, PharmD PhD
School of Population and Public Health
University of British Columbia
Vancouver, Canada
mowiens@outlook.com

Abstract

Objectives: To derive a model of paediatric post-discharge mortality following acute infectious illness.

Design: Prospective cohort study

Setting: Two hospitals in South-western Uganda.

Participants: 1307 children 6 months and 5 years admitted with a proven or suspected infection. 1242 children were discharged alive and follow-up 6 months following discharge. The six-month follow-up rate was 98.3%.

Interventions: None.

Primary and secondary outcome measures: The primary outcome was post-discharge mortality within 6 months following the initial hospital discharge

Results: 64 children died during admission (5.0%) and 61 died within six month of discharge (4.9%). Of those that died following discharge, 31 (51%) occurred within the first 30 days. The final adjusted model for the prediction of post-discharge mortality included the variables mid-upper arm circumference (OR: 0.95, 95% CI: 0.94–0.97, per 1 mm increase), time since last hospitalization (OR: 0.76, 95% CI: 0.61 – 0.93, for each increased period of no hospitalization), oxygen saturation (OR: 0.96, 95% CI: 0.93 – 0·99, per 1% increase), abnormal Blantyre coma score (OR: 2.39, 95% CI: 1·18 –4.83), and HIV positive status (OR: 2.98, 95% CI: 1.36 – 6.53). This model produced a receiver operating characteristic curve with an AUC of 0.82. With sensitivity of 80%, our model had a specificity of 66%. Approximately 35% of children would be identified as high risk (11.1% mortality risk) and the remaining would be classified as low risk (1.4% mortality risk), in a similar cohort.

Conclusions: Mortality following discharge is a poorly recognised contributor to child mortality. Identification of at-risk children is critical in developing post-discharge interventions. A simple prediction tool that uses five easily collected variables can be used to identify children at high risk of death after discharge. Improved discharge planning and care could be provided for high risk children.

Strengths and limitations of this study

The primary strengths of this study are (1) prospective and rigorous data collection and (2) near complete follow-up.

Further strengths include the derivation of multiple similar models to allow prediction in circumstances where not all variables may be available

Regression models can easily be incorporated into a mobile-health based tool for simple and rapid prediction by health workers

The primary limitations of this study are (1) relatively few outcomes and (2) lack of external validity. Despite few outcomes our models performed quite well.

These limitations highlight the need for further research on this important but neglected topic.

The identification of high risk does not imply that risk can be reduced. Further work is needed on the development of post-discharge interventions to reduce this burden.

Background

Acute infectious diseases continue to be the most important contributor to the six million children younger than five years who die every year, particularly in Africa.[1] It is widely accepted that as a global community we have fallen short in reducing under-five mortality, as demonstrated by the fact that most developing countries, especially those in sub-Saharan Africa will not achieve the fourth millennium development goal of a two-thirds reduction in child mortality.[2] An important but neglected contributor to infectious disease related mortality is the vulnerable period following hospital discharge.

A recent systematic review of pediatric studies assessing post-discharge mortality in resource poor countries and found that post-discharge mortality often exceed in-hospital mortality.[3] Thus attention to at-risk populations post discharge is sorely needed. However, while several factors were consistently found to be associated with mortality following discharge, including malnutrition, HIV and severe pneumonia, easy identification is essential in order to develop targeted post-discharge interventions. Ideally, the unacceptably high risk of morbidity and mortality following discharge suggests that all children should be afforded follow up care. However, significant resource constraints in the countries most affected by this issue preclude any significant intervention on all discharged children. Therefore, the ability to quickly and effectively identify at-risk children would be an invaluable step towards the implementation of life-saving post-discharge interventions. An important and easily identified dichotomy among hospital admissions are infectious diseases and non-infectious disease related admissions, such as trauma, cancer and congenital diseases. Although further divisions based on etiology of infection, or an underlying risk factor such as malnutrition or HIV status, may be an attractive approach in risk stratification, significant difficulties in disease definitions and often overlapping

risks makes this approach very difficult. The development of a robust yet simple risk-scoring algorithm could significantly advance a systematic and evidence based approach in post-discharge care.

The purpose of this study was to derive simple prediction models that could efficiently stratify children according to post-discharge mortality risk.

Methods

Population

Mbarara, a city of approximately 195,000, is the largest city in the Southwestern region of Uganda. This study was conducted at two hospitals in Mbarara. The Mbarara Regional Referral Hospital (MRRH) is the main referral hospital in Southwestern Uganda. It is a public hospital funded by the Uganda Ministry of Health. MRRH is associated with the Mbarara University of Science and Technology and is a primary training site for its health care graduates. The pediatric ward admits approximately 5000 patients per year. The Holy Innocents Children's Hospital (HICH) is a faith-based children's hospital offering subsidized fee-for-service outpatient and in-patient care in Mbarara. The HICH admits approximately 2500 patients per year.

This was a prospective observational study conducted between March 2012 and December 2013. This study was approved the institutional review boards at the University of British Columbia (Canada) and the Mbarara University of Science and Technology (Uganda) as well as the Uganda National Council for Science and Technology and Office of the President. Written informed consent was required for all subjects.

Eligibility

All children aged 6 months to five years who were admitted with a proven or suspected infection were eligible for enrollment. The upper age limit was chosen to coincide with the under-five target group of the millennium development goals. The lower age limit was chosen for logistic (census enrollment with limited research staff) and statistical considerations (group homogeneity). Subjects already enrolled in the study were not eligible to be enrolled during subsequent admissions.

Study procedure

Following enrollment, a research nurse obtained and recorded clinical signs including a one minute respiratory rate, blood pressure (automated), axillary temperature, Blantyre coma score, and using the Phone Oximeter [4], one mininute photoplethysmogram (PPG), blood oxygen saturation (SpO_2) and heart rate. Anthropometric data (height, weight, mid-upper arm circumference) were also measured and recorded. Age-dependent demographic variables collected at enrollment were converted to age corrected z-scores according to the World Health Organization Child Growth Standards.[5] The age corrected heart rate and respiratory rate z-scores were obtained by standardizing the raw measurements using the median and SD values provided by Fleming et al.[6] The age corrected z-scores for systolic blood pressure were calculated using subjects' height, according to the procedures previously described.[7]

A blood sample was taken for measurement of hemoglobin, HIV and a malaria blood smear (microscopy). HIV status was determined using the national rapid diagnostic test serial algorithm.[8] All positive tests on the Determine Antibody Test were confirmed by a separate test (UniGold). Children under 12 months of age with a positive test were confirmed using PCR. Hemoglobin was measured on a Beckman Coulter Ac.T Hematology analyzer.

An interview was conducted with the subject's parent/guardian and information about previous admissions, distance from health facility, transportation costs, bed-net use, maternal education, maternal age, maternal HIV status, history of sibling deaths and drinking water safety were elicited. Subjects received routine care during their hospital stay and were discharged at the discretion of the treating medical team. The discharge status of all enrolled subjects was recorded as death, referral, discharged alive, and discharged against medical advice. The diagnoses made by the medical team were also recorded. Upon discharge, families with active telephone lines were contacted at months two and four to determine the vital status of the child. Families with no telephone access received in-person follow-up by a field officer. At approximately six months following discharge all subjects received in-person follow-up. In addition to post-discharge vital status, health seeking and re-hospitalizations since the initial discharge were also recorded.

Study data were collected and managed using REDCap electronic data capture tools hosted at the Child and Family Research Institute, Vancouver, Canada.[9] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Candidate predictor variables were derived using a two-round modified Delphi approach. Briefly, 23 experts in relevant disciplines were solicited to complete an online survey and provide feedback on an initial list of proposed predictors. Predictors were evaluated on considerations of utility as predictors, availability, cost and resource related applicability. Experts were asked to provide additional potential variables which were then evaluated during a

second round of surveys. Data was evaluated by the research team and a final list of candidate predictor variables for modelling was determined.[10]

Outcomes

The primary outcome was post-discharge mortality at any time during the six month post-discharge period.

Sample size

For the derivation of prediction models, standard calculations of sample size do not apply since these calculations do not account for the model development process (i.e., selection of variables and the optimization to achieve specified sensitivity and specificity cut-offs). For this study we determined the sample size needed to validate the derived model and plan to use an equal number of patients for the derivation phase. For the validation study, assuming that the derived model achieves a sensitivity of 85% with at least 50% specificity, 100 events, corresponding to a total sample of approximately 1000 live-discharges (assuming a post-discharge mortality rate of 10%), would be needed to obtain 80% power for ensuring that the lower 95% confidence limit on sensitivity will be at least 75%. Since resources are scarce, a higher sensitivity at the expense of specificity would further limit practical application of such a model. An interim analysis of the study showed that the post-discharge mortality rate would likely not exceed 5% and enrollment was stopped when 1307 subjects were enrolled.

Statistical Analysis

All variables were assessed using univariate logistic regression to determine their level of association with the primary outcome. Continuous variables were assessed for model fit using

the Hosmer-Lemeshow test.[11] Missing data was imputed by the method of multivariate imputation by chained equations.[12] Following univariate analysis candidate models were generated using a step-wise selection procedure minimizing Akaike's Information Criterion (AIC). This method is considered asymptotically equivalent to cross-validation and bootstrapping.[13,14] All models generated in this sequence having AIC values within 10% of the lowest value were considered as reasonable candidates. The final selection of a model was judged on model parsimony (the simpler the better), availability of the predictors (with respect to minimal resources and cost), and the attained sensitivity (with at least 50% specificity). All analyses were conducted using SAS 9.3 (Carey, NC, USA) and R 3.1.3 (Vienna, Austria; http://www.R-project.org). Additional models were created using the above process but with the absence of key variables used in deriving the primary model, including a model not including any variables likely to change over the course of admission. This was done to increase application in a variety of settings were certain variables may not be available.

Results

During the period of study 1822 subjects were screened for eligibility, of which 516 (28%) were excluded. Reasons for exclusion included isolated malnutrition (n=192), re-admission of previously enrolled subject (n=51), refusal of consent (n=22), cardiac disease (n=19), poisoning/drug reaction (n=19), cancer (n=12) as well as a plethora of other non-infectious admissions (n=165). One thousand three hundred and seven (1307) subjects admitted with a presumed or proven infection were enrolled at the time of their admission. During the course of admission 64 (5.1%) subjects died, and 1242 (94.9%) were discharged alive (**Figure 1**). Among the children discharged 54% were male, and the median age was 18.1 months (IQR 10.8 – 34.6). Pneumonia, malaria and gastroenteritis were the most common clinical discharge diagnoses and

were present in 31%, 50%, and 8% of discharged subjects respectively. According to anthropometric variables collected at admission, 30% of subjects were considered underweight (Weight for age z-score less than -2), 35% were considered wasted (weight for height/length z-score less than -2) and 29% were considered stunted (height/length for age z-score less than -2) (**Table 1**). Missing observations were minimal (**Table 2**).

Post-discharge mortality

The rate of successful follow-up during the post-discharge period was 98.3%, with only 6 subjects receiving no follow-up during this period. Overall, 61 (4.9%) children died following discharge. Of those that died, the median time to death was 30 days (IQR 7 – 81). Of the 61 deaths, 41 (67%) occurred outside of a hospital and 20 (33%) occurred during a hospital re-admission. Thirty variables were tested for univariate associations with post-discharge mortality (**Table 2**). Mid-upper arm circumference was the variable with the highest area under the receiver operating characteristic curve, 0.76 (95% CI 0.70 – 0.83) and was highly significant ($p < 0.0001$). Other anthropometric variables, including weight for age z-score, length/height for age z-score, and weight for length/height z-score were also highly associated with post-discharge mortality but had much lower areas under the ROC curve. Oxygen saturation was the most predictive of the non-anthropometric variables, with an area under the ROC curve of 0.65 (95% CI 0.57 – 0.73), followed by age and parasitemia with areas under the ROC curve of 0.64 (95% CI 0.56 – 0.70) and 0.60 (95% CI 0.55 – 0.65), respectively. Other variables achieving statistical significance, but showing lower areas under the ROC curve included systolic blood pressure, axillary temperature, HIV status, abnormal Blantyre coma score (yes vs no), duration of illness prior to admission greater than 7 days and time since last hospitalization. Hemoglobin level,

history of sibling deaths, maternal HIV status, maternal education and distance from admitting health facility were not associated with post-discharge mortality in the univariate analysis.

Multivariate prediction models

One primary model and three alternate models of equal sensitivity were developed for the prediction of six-month post discharge mortality (**Table 3**). Two alternate models were developed while systematically excluding oxygen saturation, and HIV status, respectively, since these may not be routinely available in all clinical settings. A fourth model was developed excluding variables most likely to change over the course of admission (i.e. clinical variables), giving the model utility for variables collected at any time throughout the hospital stay. The primary model included mid-upper arm circumference in mm (MUAC), oxygen saturation (SpO2) at admission (percent), time since previous hospitalization, the presence of abnormal Blantyre coma score (BCS) at admission, and HIV status. The area under the receiver operator characteristic curve was 0.82 (95% CI 0.76 – 0.87) (**Figure 2**). The model, at a cut-off of greater than 80% sensitivity, had a final sensitivity of 82% (95% CI 0.75 – 0.87) and a specificity of 66% (95% CI 64 – 69). In a population similar to this model derivation cohort we would expect the positive predictive value to be 11.1%, and the negative predictive value to be 98.6% (**Table 4)**. The final model equation for the primary model was: logit(p) = 7.71 + (-0.041; MUAC) + (-0.041; SpO2) + (-0.28; time period since last hospitalization) + (1.09; HIV positive) + (0.87; BCS <5).

Model two excluded oxygen saturation (**Table 3**). The final model included mid-upper arm circumference, time since last hospitalization, HIV status and the presence of an abnormal Blantyre coma score. The area under the ROC curve was 0.81 (95% CI 0.75 – 0.87). This model

had a sensitivity of 80% (70 – 90) and specificity of 68% (95% CI 65 – 70) and would generate a positive and negative predictive value of 11.3% and 98.5%, respectively, in a population similar to the derivation cohort

The third model excluded HIV status (**Table 3**). This model had a final area under the ROC curve of 0.80 (95% CI 0.74 – 0.86) and a sensitivity of 80% (95%CI 70 – 90) and specificity of 63% (95% CI 60 – 66). The positive and negative predictive values were 10.2% and 98.4%, respectively.

The final model excluded all time changing clinical parameters (ex. Vital signs, SpO2, coma score etc.) so as to be applicable to data collected at any time during admission, including discharge. This model contained only three variables, MUAC, HIV status and the since the most recent hospitalization. This model achieved good performance characteristics including an AUC of 0.80 (95% CI 0.73 – 0.86). The sensitivity was specificity was 82% (95% CI 72 – 92) and the specificity was 61% (95% CI 59 – 64) and the positive and negative predictive values were 9.9% and 98.5%, respectively.

Discussion

This study represents the first systematic approach to the development of a simple risk-scoring algorithm for post-discharge mortality following admission for an acute infectious illness using prospectively collected data. The variables used in these models are easy to collect and include mid-upper arm circumference, oxygen saturation, Blantyre coma score, time since last hospitalization, and HIV status. Four prediction models were developed to ensure its effective application in a variety of clinical circumstances. The models which were developed use only variables collected at admission and can therefore easily be incorporated into the discharge

planning process during the hospital stay. Using these models, the identification of at-risk children would ensure that most children likely to die in the post-discharge period (about 80%) would be identified. These children have an average mortality risk of approximately over 10%, justifying the exploration of potentially life-saving interventions. Interventions found to be effective could likely be brought to scale without inordinately burdening already stressed health systems.

The development and implementation of predictive models into routine clinical care is not common in resource poor countries. The high prevalence of overlapping diseases (such as pneumonia, malaria and malnutrition), and the difficulty in creating reliable diagnostic algorithms to identify eligible populations, create significant difficulty in the application of disease specific models. To create models with uptake potential they would need to be linked with existing clinical practices and resources and would also require a shift in how infectious illness is viewed, not as an episodic diseases but as a continuum beyond the acute episode. The Integrated Management of Childhood Illness (IMCI), while not a predictive tool *per se*, is an algorithm-based approach for the diagnosis and management of acute infectious illnesses.[15] IMCI has seen significant uptake in many countries throughout Sub-Saharan Africa, and has provided a systematic approach to the care of children within health facilities. More importantly, it has been shown to improve care in the regions where it has been implemented.[16] However, the IMCI does not address the important issue of post-discharge vulnerability and therefore fails to provide any guidance beyond the period of acute illness in the hospital, even though the post discharge period will claim as many lives as the acute hospital period. The integration of a post-discharge risk score into IMCI could begin to address this need.

This study is subject to several limitations. A primary limitation of this study is the relatively low number of outcomes observed. Although our initial sample size estimates were to observe 100 outcomes, we only observed 61. Our comprehensive follow-up of subjects ensured that missed outcomes are unlikely. Further, the performance of our model was good, with the lower limits of the calculated 95% confidence intervals for AUC, sensitivity and specificity remaining in an acceptable range. A further limitation is the lack of external validity. While our research sites represented the typical East African context, further research is required to ensure the validity of these models elsewhere, especially in areas with significant differences in the distribution of important diseases such as malaria, diarrhea and pneumonia and malnutrition. A limitation to application of the prediction models developed is that the risk score is based on a regression equation and cannot be easily computed without the assistance of a computer or similar device. However, with the increasing prevalence of mobile phones in developing countries, health interventions are increasingly focused on utilizing the computational power of mobile phones to implement life-saving technology. Several important health interventions use mobile technology to improve care.[17–19]

It is clear that malnutrition plays a major role in post-discharge mortality. Mid-upper arm circumference provided a significant proportion of the predictive power in our models, alone providing an AUC of 0.76, only 7% lower than the final full model. No models meeting our pre-specified criteria could be developed without the use of any anthropomorphic measure. The importance of malnutrition has also been clearly demonstrated in other studies of post-discharge mortality.[20–22] Although first described over 50 years ago, environmental enteropathy (also called tropical enteropathy or environmental enteric dysfunction) has received significant attention in recent years. It has been suggested that changes in the gut microbiome and the small intestinal

wall (flattened villi, inflammation and increased permeability) soon after birth can lead to early and irreversible stunting, frequent diarrheal illness and persistent systemic sub-clinical inflammation.[23–26] This appears to promote a vicious cycle of infection and malnutrition. While difficult to address, a focus on nutrition (micronutrient and macronutrient) before, during and following the acute phase of illness may reduce the exacerbation of this cycle. Half of the children who died during the course of this study did so more than 30 days following discharge. Therefore, emphasis must also be placed on preventing re-infection in vulnerable children. Promotion of good health behavior (including hygiene) during the post-discharge period is therefore likely to play an important role.

One further area for intervention is education on timely health seeking. Sixty-seven percent of the deaths in this study occurred outside of a hospital context, but 28% of the out-of hospital deaths occurred on the way to hospital. The education of mothers on the early warning signs of recurrent illness should also be emphasized during discharge since the common perception may be that recovery from infection brings a child back to a baseline level of risk, which is clearly not true. Since all children were enrolled during a hospital admission, physical inaccessibility was generally not an initial barrier. A previous study on the hospital burden of pediatric acute lower respiratory infections found that although 62% of children are treated in the hospital, 80% of deaths occur outside of the hospital.[27] While this study did not address the timing of the out-of-hospital deaths in relation to the hospital visit, it is possible that many of these deaths occurred in the vulnerable months following discharge.

Conclusion

This study has derived a parsimonious risk-scoring tool for pediatric post-discharge mortality. Further work is required in external validation of this tool and the development of effective post-discharge interventions.

Figure 1 caption

Figure 1. Consort diagram of study flow

Figure 2 caption

Figure 2. Performance of the primary prediction model derived with data from admission. ROC = receiver operating characteristic. Sens = sensitivity. Spec = specificity. NPV = negative predictive value. PPV = positive predictive value.

Table 1. General Characteristics of discharged subjects (N=1242)

Characteristic	**Frequency**
Age < 12m	378 (30%)
Age 12m – 24m	379 (30%)
Age 24m – 36m	198 (16%)
Age 36m - 48m	150 (12%)
Age > 48m	138 (11%)
Male sex	682 (55%)
Length of stay < 3 days	487 (39%)
Length of stay 3 – 5 days	487 (39%)
Length of stay 6 – 10 days	173 (14%)
Length of stay > 10 days	96 (8%)
Discharge AMA	120 (10%)
Diagnoses	
Pneumonia	390 (31%)
Clinical malaria	621 (50%)
Parasitemia	418 (34%)
Gastroenteritis	96 (8%)
SSTI	7 (0.5%)
Meningitis	32 (2.5%)
Tuberculosis	17 (1.4%)
Measles	15 (1.2%)
Comorbidities	
HIV	58 (4.7%)
Sickle Cell	7 (0.5%)
Tuberculosis	21 (1.7%)
Admission Anthropometric Characteristics	
Underweight (WAZ <-2)	347 (30%)
Severe underweight (WAZ <-3)	188 (15%)
Wasting (WHZ <-2)	436 (35%)
Severe Wasting (WHZ <-3)	232 (17%)
Stunting (HAZ < -2)	357 (29%)
Severe Stunting (HAZ < -3)	187 (15%)
MUAC < 125	183 (15%)
MUAC < 115	96 (7.7%)

AMA = against medical advice; WAZ = weight for age z-score; WHZ = weight for height/length z-score; HAZ = height/length for age z-score; MUAC = mid-upper arm circumference

Table 2. Univariate analysis of potential predictor variables

Variable	Missing obs.	OR (95% CI)	AUC (95% CI)	P value
Male sex	0	0.90 (0.54 - 1.51)	0.51 (0.45 – 0.58)	0.700
Age (months)	3	0.97 (0.97 - 0.97)	0.64 (0.56 – 0.70)	0.003
MUAC (mm)	14	0.97 (0.96 - 0.98)	0.76 (0.70 – 0.83)	<0.001
Weight for age z-score	5	0.66 (0.57 - 0.76)	0.68 (0.60 – 0.76)	<0.001
Weight for length/height z-score	15	0.81 (0.72 - 0.91)	0.62 (0.55 – 0.70)	<0.001
Length/height for age z-score	16	0.79 (0.70 - 0.89)	0.63 (0.56 – 0.71)	<0.001
HR-age z-score	3	0.86 (0.74 - 0.99)	0.61 (0.53 – 0.69)	0.036
HR (raw)	0	1.00 (0.99 - 1.01)	0.53 (0.47 – 0.62)	0.728
RR-age z-score	3	0.99 (0.92 - 1.06)	0.53 (0.45 – 0.60)	0.747
RR (raw)	0	1.01 (1.00 - 1.03)	0.57 (0.50 – 0.63)	0.100
SBP z-score	21	0.94 (0.79 - 1.12)	0.50 (0.45 – 0.61)	0.526
SBP (raw)	6	0.98 (0.96 – 1.00)	0.58 (0.50 – 0.66)	0.018
DBP (raw)	6	0.99 (0.97 - 1.01)	0.55 (0.50 – 0.65)	0.255
Temperature (transformed)	0	1.02 (0.90 - 1.16)	0.51 (0.45 – 0.57)	0.789
Temperature (raw)	0	0.76 (0.62 - 0.93)	0.58 (0.50 – 0.65)	0.007
SpO2 (raw)	13	0.94 (0.92 - 0.96)	0.65 (0.57 – 0.73)	<0.001
SpO2 (transformed)	13	1.04 (1.02 - 1.05)	0.65 (0.57 – 0.73)	<0.001
HIV positive (vs neg.)	25	5.21 (2.55 - 10.65)	0.57 (0.52 – 0.62)	<0.001
Hemoglobin (g/dL)	10	0.95 (0.87 - 1.03)	0.56 (0.49 – 0.63)	0.227
Blantyre coma scale <5 (vs 5)	0	2.40 (1.27 - 4.57)	0.56 (0.50 – 0.61)	0.007
Positive blood smear (vs neg.)	11	0.33 (0.16 - 0.68)	0.60 (0.55 – 0.65)	0.002
Illness > 7 days prior to admission	1	0.50 (0.30 - 0.83)	0.58 (0.52 – 0.65)	0.008
Time since last hospitalization[§]	3	0.75 (0.62 – 0.90)	0.59 (0.52 – 0.67)	0.003
Sibling deaths	0	1.54 (0.89 - 2.65)	0.55 (0.48 – 0.61)	0.121
Number of children in family	2	1.02 (0.92 - 1.13)	0.50 (0.43 – 0.58)	0.750
Boil all drinking water	0	0.82 (0.47 - 1.42)	0.52 (0.46 – 0.58)	0.471
Maternal Age (years)	0	1.00 (0.97 - 1.04)	0.52 (0.41 – 0.57)	0.892
Maternal HIV (ref: neg.)				
HIV positive, n=142	0	1.79 (0.87 - 3.67)	0.54 (0.48 – 0.61)	0.113
HIV status unknown, n=220	0	1.27 (0.64 - 2.52)		0.499
Maternal Education (ref: < Primary 3)				
Primary 3 – Primary 7, n=630	0	1.18 (0.62 - 2.23)		0.619
Some Secondary, n=269	0	0.72 (0.31 - 1.70)	0.54 (0.50 – 0.63)	0.457
Post-secondary, n=93	0	1.18 (0.41 - 3.36)		0.762
Bednet use (ref = never)				
Sometimes	0	1.00 (0.48 - 2.09)	0.52 (0.45 – 0.59)	0.996
Always	0	0.85 (0.46 - 1.58)		0.612
Distance from hospital (ref: < 30 min.)				
30 to 60 minutes	0	0.71 (0.31 - 1.64)	0.56 (0.49 – 0.62)	0.421
More than 60 minutes	0	1.30 (0.70 - 2.41)		0.401

§ ordered as <7d, 7 – 30d, 30d – 1yr and never (analyzed as continuous)

MUAC = mid-upper arm circumference; HR = heart rate; RR= respiratory rate; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 3. Models developed for prediction of 6 month post-discharge mortality

Variable	Regression Estimate	p-value	OR (95% CI)
Model 1 – Primary model, Intercept = 7.7172			
MUAC	-0.0462	<0.0001	0.95 (0.94 – 0.97)
SpO2	-0.0411	0.0029	0.96 (0.93 – 0.99)
Time since last hosp.	-0.2775	0.0085	0.76 (0.62 – 0.93)
HIV positive	1.0915	0.0064	2.98 (1.36 – 6.53)
Abnormal BCS	0.8723	0.0150	2.39 (1.18 – 4.83)
Model 2 – Model without SpO2, Intercept = 4.4538			
MUAC	-0.0505	<0.0001	0.95 (0.94 – 9.97)
Time since last hosp.	-0.2503	0.0153	0.78 (0.64 – 0.95)
HIV positive	1.0902	0.0061	2.98 (1.37 – 6.48)
Abnormal BCS	1.0664	0.0022	2.91 (1.47 – 5.75)
Model 4 – Model without HIV, Intercept = 8.2813			
MUAC	-0.0492	<.0001	0.95 (0.94 – 0.97)
SpO2	-0.0412	0.0027	0.96 (0.93 – 0.99)
Time since last hosp.	-0.2870	0.0058	0.75 (0.61 – 0.92)
Abnormal BCS	0.8040	0.0248	2.23 (1.11 – 4.51)
Model 4 – Model without clinical variables, Intercept = 4.4511			
MUAC	-0.0492	<.0001	0.95 (0.94 – 0.97)
HIV positive	1.0143	0.0108	2.76 (1.26 – 6.01)
Time since last hosp.	-0.2458	0.0164	0.78 (0.64 – 0.96)

MUAC = mid-upper arm circumference; BCS = Blantyre coma score

Table 4. Model Characteristics at probability cut-offs ensuring model sensitivity of greater than 80%

Model	AUC (95% CI)	Prob. cut-off	Sens. (95% CI)	Spec. (95% CI)	PPV	NPV
1	0.82 (0.75 – 0.87)	0.035	82.0 (72.3 – 91.6)	66.2 (63.5 – 68.9)	11.1	98.6
2	0.81 (0.75 – 0.87)	0.040	80.3 (70.4 – 90.3)	67.5 (64.8 – 70.2)	11.3	98.5
3	0.80 (0.74 – 0.86)	0.031	80.3 (70.4 – 90.3)	63.4 (60.7 – 66.2)	10.2	98.4
4	0.80 (0.73 – 0.86)	0.035	82.0 (72.3 – 91.6)	61.4 (58.6 – 64.2)	9.9	98.5

AUC = area under the receiver operator characteristic curve; Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value

Acknowledgments: We gratefully acknowledge the contributions of Annet Twinomuguni, Justine Kamazima, Agaba Collins, Clare Komugisha, Solome Kobugyenyi, Alexander Mutungi and Hassan Bariahikwa. Without their dedication this study could not have been completed

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: This study was internally funded. M Wiens was supported by a fellowship from the Canadian Institutes of Health Research, the Michael Smith Foundation for Health research and the Canadian Child Health Clinician Scientist Program.

Contributor Statement

MO Wiens: Contributed to design, data collection, analysis, drafting of initial manuscript, reviewing and revising manuscript, and approval final manuscript

E Kumbakumba: Contributed to design, data collection, interpretation, reviewing and revising manuscript, and approved final manuscript

CP Larson: Contributed to design, interpretation, reviewing and revising manuscript, and approved final manuscript

JM Ansermino: Contributed to design, data collection, analysis, reviewing and revising manuscript, and approved final manuscript

J Singer: Contributed to design, analysis, reviewing and revising manuscript, and approved final manuscript

N Kissoon: Contributed to design, reviewing and revising manuscript, and approved final manuscript

H Wong: Contributed to design, analysis, reviewing and revising manuscript, and approved final manuscript

A Ndamira: Contributed to design, reviewing and revising manuscript, and approved final manuscript

J Kabakyenga: Contributed to design, reviewing and revising manuscript, and approved final manuscript

J Kiwanuka: Contributed to design, reviewing and revising manuscript, and approved final manuscript

G Zhou: Contributed to analysis, reviewing and revising manuscript, and approved final manuscript

Data Sharing: No additional data available

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430–40.

2. Wang H, Liddell C a, Coates MM, Mooney MD, Levitz CE, Schumacher AE, et al. Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;957–79.

3. Wiens M, Pawluk S, Kissoon N. Pediatric Post-Discharge Mortality in Resource Poor Countries: A Systematic Review. PLoS One [Internet]. 2013 Jan [cited 2014 Jun 19];8(6):e66698.

4. Karlen W, Dumont G, Petersen C, Gow J, Lim J, Sleiman J, et al. Human-centered phone oximeter interface design for the operating room: Pulse Oximeter Interfaced to a Mobile Device for Anesthesia Monitoring in the Developing World. Proceedings of the International Conference on Health Informatics. Rome, Italy: SciTePress; 2011. p. 433–8.

5. The WHO Child Growth Standards [Internet]. 2006 [cited 2015 Mar 1]. Available from: http://www.who.int/childgrowth/standards/en/

6. Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, MacOnochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: A systematic review of observational studies. Lancet. 2011;377(9770):1011–8.

7. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114:555–76.

8. National Implementation Guidelines for HIV Counselling and Testing in Uganda [Internet]. Kampala, Uganda; 2010. Available from: http://library.health.go.ug/publications

9. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.

10. Wiens MO, Kissoon N, Kumbakumba E, Singer J, Moschovis P, Ansermino JM, et al. Selecting candidate predictor variables for the modelling of post-discharge mortality: A protocol development project. Submitted. 2015.

11. Hosmer DW, Lemeshow S. Goodness of fit tests for the multiple logistic regression model. Commun Stat - Theory Methods. 1980;9(10):1043–69.

12. Van Buuren S, Groothuis-Oudshoorn K. Multivariate Imputation by Chained Equations. J Stat Softw. 2011;45(3):1–67.

13. Stone M. An Asymptotic Equivalence of Choice of Model by Cross-Validation and Akaike's Criterion. J R Stat Soc Ser B-Methodological. 1977;39(1):44–7.

14. Shibata R. Bootstrap estimate of Kullback-Leibler information for model selection. Stat Sin. 1997;7:375–94.

15. World Health Organization. Integrated Management of Childhood Illness: distance learning course. Geneva: World Health Organization; 2014.

16. Nguyen DTK, Leung KK, McIntyre L, Ghali W a., Sauve R. Does Integrated Management of Childhood Illness (IMCI) Training Improve the Skills of Health Workers? A Systematic Review and Meta-Analysis. PLoS One. 2013;8(6).

17. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet [Internet]. Elsevier Ltd; 2010;376(9755):1838–45.

18. Obasola OI, Mabawonku I, Lagunju I. A Review of e-Health Interventions for Maternal and Child Health in Sub-Sahara Africa. Matern Child Health J. 2015;In press. Available from: http://link.springer.com/10.1007/s10995-015-1695-0

19. Mitchell M, Hedt-Gauthier BL, Msellemu D, Nkaka M, Lesh N. Using electronic technology to improve clinical care - results from a before-after cluster trial to evaluate assessment and classification of sick children according to Integrated Management of Childhood Illness (IMCI) protocol in Tanzania. BMC Med Inform Decis Mak. BMC Medical Informatics and Decision Making; 2013;13(1):95.

20. Moïsi JC, Gatakaa H, Berkley JA, Maitland K, Mturi N, Newton CR, et al. Excess child mortality after discharge from hospital in Kilifi, Kenya: a retrospective cohort analysis. Bull World Health Organ. 2011;89(10):725–32.

21. Islam MA, Rahman MM, Mahalanabis D, Rahman a K. Death in a diarrhoeal cohort of infants and young children soon after discharge from hospital: risk factors and causes by verbal autopsy. J Trop Pediatr. 1996 Dec;42(6):342–7.

22. West TE, Goetghebuer T, Milligan P, Mulholland EK, Weber MW. Long-term morbidity and mortality following hypoxaemic lower respiratory tract infection in Gambian children. Bull World Health Organ. 1999 Jan;77(2):144–8.

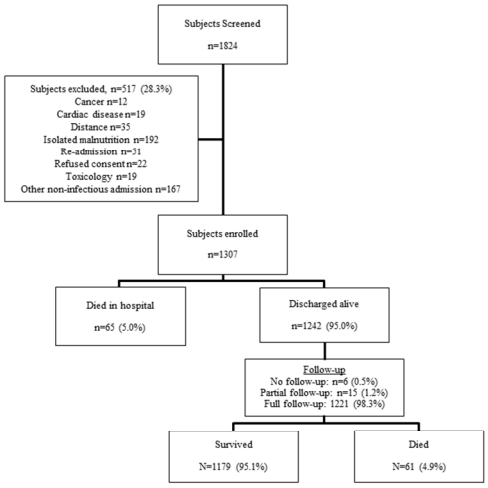
23. Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. Am J Trop Med Hyg. 2012;86(5):756–63.

24. Keusch GT, Denno DM, Black RE, Duggan C, Guerrant RL, Lavery J V, et al. Environmental Enteric Dysfunction: Pathogenesis, Diagnosis, and Clinical Consequences. Clin Infect Dis. 2014;59(Suppl 4):207–12.

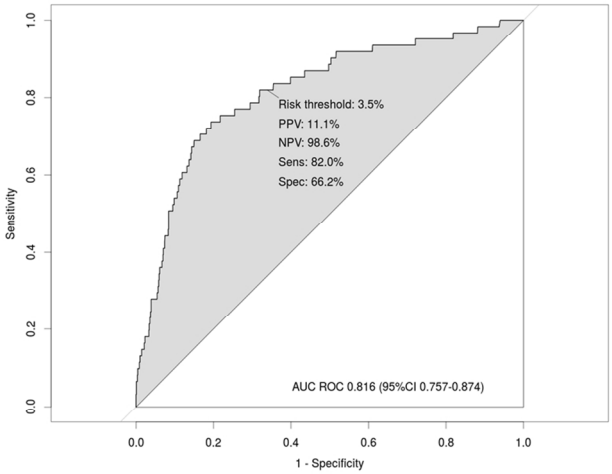
25. Kosek M, Guerrant RL, Kang G, Yori PP, Gratz J, Gottlieb M, et al. Assessment of Environmental Enteropathy in the MAL-ED Cohort Study: Theoretical and Analytic Framework. Clin Infect Dis. 2014;59(Suppl 4):239–47.

26. Jones KD, Thitiri J, Ngari M, Berkley JA. Childhood malnutrition: Toward an understanding of infections, inflammation, and antimicrobials. Food Nutr Bull. 2014;35(2):64–70.

27. Nair H, Simões E a F, Rudan I, Gessner BD, Azziz-Baumgartner E, Zhang JSF, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet. 2013 Apr 20;381(9875):1380–90.



338x190mm (96 x 96 DPI)



338x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			10

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	11/12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11/12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11/12
		(*b*) Report category boundaries when continuous variables were categorized	11/12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			13
Key results	18	Summarise key results with reference to study objectives	13
Limitations			15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Post-Discharge Mortality in Children with Acute Infectious Diseases: Derivation of Post-Discharge Mortality Prediction Models

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009449.R1
Article Type:	Research
Date Submitted by the Author:	08-Sep-2015
Complete List of Authors:	Wiens, Matthew; University of British Columbia, School of Population and Public Health Kumbakumba, Elias; Mbarara University of Science and Technology, Department of Pediatrics Larson, Charles P ; University of British Columbia, Department of Pediatrics/Centre for International Child Health, BC Children's Hospital Ansermino, Mark; University of British Columbia, Department of Pediatric Anesthesia Singer, Joel; University of British Columbia, School of Population and Public Health Kissoon, Niranjan; University of British Columbia, Department of Pediatrics Wong, Hubert; University of British Columbia, School of Population and Public Health Ndamira, Andrew; Mbarara University of Science and Technology, Department of Pediatarics Kabakyenga, Jerome; Mbarara University of Science and Technology, Maternal, Newborn and Child health Institute Kiwanuka, Julius; Mbarara University of Science and Technology, Department of Pediatarics Zhou, Guohai; University of British Columbia, Department of Statistics
Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Infectious diseases, Paediatrics
Keywords:	PAEDIATRICS, EPIDEMIOLOGY, Paediatric infectious disease & immunisation < PAEDIATRICS

Post-Discharge Mortality in Children with Acute Infectious Diseases: Derivation of Post-Discharge Mortality Prediction Models

MO Wiens[1], E Kumbakumba[2], CP Larson[3], JM Ansermino[4], J Singer[1,6], N Kissoon[5], H Wong[1], A Ndamira[2], J Kabakyenga[7], J Kiwanuka[2], G Zhou[8]

1. School of Population and Public Health, University of British Columbia, Vancouver, Canada
2. Department of Pediatrics, Mbarara University of Science and Technology, Mbarara, Uganda
3. Center for International Child Health, BC Children's Hospital, Child and Family Research Institute, Vancouver Canada
4. Department of Pediatric Anesthesiology, BC Children's Hospital and University of British Columbia, Vancouver, Canada
5. Department of Pediatrics, BC Children's Hospital and University of British Columbia, Vancouver, Canada
6. Canadian HIV Trials Network, St. Paul's Hospital and University of British Columbia, Vancouver, Canada
7. Maternal, Newborn and Child Health Institute, Mbarara University of Science and Technology, Mbarara, Uganda
8. Department of statistics, University of British Columbia, Vancouver, Canada

Word count: 3344

Correspondence to:

Matthew Wiens, PharmD PhD
School of Population and Public Health
University of British Columbia
Vancouver, Canada
mowiens@outlook.com

Abstract

Objectives: To derive a model of paediatric post-discharge mortality following acute infectious illness.

Design: Prospective cohort study

Setting: Two hospitals in South-western Uganda.

Participants: 1307 children 6 months and 5 years admitted with a proven or suspected infection. 1242 children were discharged alive and follow-up 6 months following discharge. The six-month follow-up rate was 98.3%.

Interventions: None.

Primary and secondary outcome measures: The primary outcome was post-discharge mortality within 6 months following the initial hospital discharge

Results: 64 children died during admission (5.0%) and 61 died within six month of discharge (4.9%). Of those that died following discharge, 31 (51%) occurred within the first 30 days. The final adjusted model for the prediction of post-discharge mortality included the variables mid-upper arm circumference (OR: 0.95, 95% CI: 0.94–0.97, per 1 mm increase), time since last hospitalization (OR: 0.76, 95% CI: 0.61 – 0.93, for each increased period of no hospitalization), oxygen saturation (OR: 0.96, 95% CI: 0.93 – 0·99, per 1% increase), abnormal Blantyre coma score (OR: 2.39, 95% CI: 1·18 –4.83), and HIV positive status (OR: 2.98, 95% CI: 1.36 – 6.53). This model produced a receiver operating characteristic curve with an AUC of 0.82. With sensitivity of 80%, our model had a specificity of 66%. Approximately 35% of children would be identified as high risk (11.1% mortality risk) and the remaining would be classified as low risk (1.4% mortality risk), in a similar cohort.

Conclusions: Mortality following discharge is a poorly recognised contributor to child mortality. Identification of at-risk children is critical in developing post-discharge interventions. A simple prediction tool that uses five easily collected variables can be used to identify children at high risk of death after discharge. Improved discharge planning and care could be provided for high risk children.

Strengths and limitations of this study

The primary strengths of this study are (1) prospective and rigorous data collection and (2) near complete follow-up.

Further strengths include the derivation of multiple similar models to allow prediction in circumstances where not all variables may be available

Regression models can easily be incorporated into a mobile-health based tool for simple and rapid prediction by health workers

The primary limitations of this study are (1) relatively few outcomes and (2) lack of external validity. Despite few outcomes our models performed quite well.

These limitations highlight the need for further research on this important but neglected topic.

The identification of high risk does not imply that risk can be reduced. Further work is needed on the development of post-discharge interventions to reduce this burden.

Background

Acute infectious diseases continue to be the most important contributor to the six million children younger than five years who die every year, particularly in Africa.[1] It is widely accepted that as a global community we have fallen short in reducing under-five mortality, as demonstrated by the fact that most developing countries, especially those in sub-Saharan Africa will not achieve the fourth millennium development goal of a two-thirds reduction in child mortality.[2] An important but neglected contributor to infectious disease related mortality is the vulnerable period following hospital discharge.

A recent systematic review of pediatric studies assessing post-discharge mortality in resource poor countries and found that post-discharge mortality often exceed in-hospital mortality.[3] Thus attention to at-risk populations post discharge is sorely needed. However, while several factors were consistently found to be associated with mortality following discharge, including malnutrition, HIV and severe pneumonia, easy identification is essential in order to develop targeted post-discharge interventions. Ideally, the unacceptably high risk of morbidity and mortality following discharge suggests that all children should be afforded follow up care. However, significant resource constraints in the countries most affected by this issue preclude any significant intervention on all discharged children. Therefore, the ability to quickly and effectively identify at-risk children would be an invaluable step towards the implementation of life-saving post-discharge interventions. An important and easily identified dichotomy among hospital admissions are infectious diseases and non-infectious disease related admissions, such as trauma, cancer and congenital diseases. Although further divisions based on etiology of infection, or an underlying risk factor such as malnutrition or HIV status, may be an attractive approach in risk stratification, significant difficulties in disease definitions and often overlapping

risks makes this approach very difficult. The development of a robust yet simple risk-scoring algorithm could significantly advance a systematic and evidence based approach in post-discharge care.

The purpose of this study was to derive simple prediction models that could efficiently stratify children according to post-discharge mortality risk.

Methods

Population

Mbarara, a city of approximately 195,000, is the largest city in the Southwestern region of Uganda. This study was conducted at two hospitals in Mbarara. The Mbarara Regional Referral Hospital (MRRH) is the main referral hospital in Southwestern Uganda. It is a public hospital funded by the Uganda Ministry of Health. MRRH is associated with the Mbarara University of Science and Technology and is a primary training site for its health care graduates. The pediatric ward admits approximately 5000 patients per year. The Holy Innocents Children's Hospital (HICH) is a faith-based children's hospital offering subsidized fee-for-service outpatient and in-patient care in Mbarara. The HICH admits approximately 2500 patients per year.

This was a prospective observational study conducted between March 2012 and December 2013. This study was approved the institutional review boards at the University of British Columbia (Canada) and the Mbarara University of Science and Technology (Uganda) as well as the Uganda National Council for Science and Technology and Office of the President. This study was voluntary and written informed consent was provided by a parent or guardian of all children who were enrolled.

Eligibility

All children aged 6 months to five years who were admitted with a proven or suspected infection were eligible for enrollment. The upper age limit was chosen to coincide with the under-five target group of the millennium development goals. The lower age limit was chosen for logistic (census enrollment with limited research staff) and statistical considerations (group homogeneity). Subjects already enrolled in the study were not eligible to be enrolled during subsequent admissions.

Study procedure

Following enrollment, a research nurse obtained and recorded clinical signs including a one minute respiratory rate, blood pressure (automated), axillary temperature, Blantyre coma score, and using the Phone Oximeter [4], one mininute photoplethysmogram (PPG), blood oxygen saturation (SpO_2) and heart rate. Anthropometric data (height, weight, mid-upper arm circumference) were also measured and recorded. Age-dependent demographic variables collected at enrollment were converted to age corrected z-scores according to the World Health Organization Child Growth Standards.[5] The age corrected heart rate and respiratory rate z-scores were obtained by standardizing the raw measurements using the median and SD values provided by Fleming et al.[6] The age corrected z-scores for systolic blood pressure were calculated using subjects' height, according to the procedures previously described.[7]

A blood sample was taken for measurement of hemoglobin, HIV and a malaria blood smear (microscopy). HIV status was determined using the national rapid diagnostic test serial algorithm.[8] All positive tests on the Determine Antibody Test were confirmed by a separate test

(UniGold). Children under 12 months of age with a positive test were confirmed using PCR. Hemoglobin was measured on a Beckman Coulter Ac.T Hematology analyzer.

An interview was conducted with the subject's parent/guardian and information about previous admissions, distance from health facility, transportation costs, bed-net use, maternal education, maternal age, maternal HIV status, history of sibling deaths and drinking water safety were elicited. Subjects received routine care during their hospital stay and were discharged at the discretion of the treating medical team. The discharge status of all enrolled subjects was recorded as death, referral, discharged alive, and discharged against medical advice. The diagnoses made by the medical team were also recorded. Upon discharge, families with active telephone lines were contacted at months two and four to determine the vital status of the child. Families with no telephone access received in-person follow-up by a field officer. At approximately six months following discharge all subjects received in-person follow-up. In addition to post-discharge vital status, health seeking and re-hospitalizations since the initial discharge were also recorded.

Study data were collected and managed using REDCap electronic data capture tools hosted at the Child and Family Research Institute, Vancouver, Canada.[9] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Candidate predictor variables were derived using a two-round modified Delphi approach. Briefly, 23 experts in relevant disciplines were solicited to complete an online survey and

provide feedback on an initial list of proposed predictors. Predictors were evaluated on considerations of utility as predictors, availability, cost and resource related applicability. Experts were asked to provide additional potential variables which were then evaluated during a second round of surveys. Data was evaluated by the research team and a final list of candidate predictor variables for modelling was determined.[10]

Outcomes

The primary outcome was post-discharge mortality at any time during the six month post-discharge period.

Sample size

For the derivation of prediction models, standard calculations of sample size do not apply since these calculations do not account for the model development process (i.e., selection of variables and the optimization to achieve specified sensitivity and specificity cut-offs). For this study we determined the sample size needed to validate the derived model and plan to use an equal number of patients for the derivation phase. For the validation study, assuming that the derived model achieves a sensitivity of 85% with at least 50% specificity, 100 events, corresponding to a total sample of approximately 1000 live-discharges (assuming a post-discharge mortality rate of 10%), would be needed to obtain 80% power for ensuring that the lower 95% confidence limit on sensitivity will be at least 75%. Since resources are scarce, a higher sensitivity at the expense of specificity would further limit practical application of such a model. An interim analysis of the study showed that the post-discharge mortality rate would likely not exceed 5% and enrollment was stopped when 1307 subjects were enrolled.

Statistical Analysis

All variables were assessed using univariate logistic regression to determine their level of association with the primary outcome. Continuous variables were assessed for model fit using the Hosmer-Lemeshow test.[11] Missing data was imputed by the method of multivariate imputation by chained equations.[12] Following univariate analysis candidate models were generated using a step-wise selection procedure minimizing Akaike's Information Criterion (AIC). This method is considered asymptotically equivalent to cross-validation and bootstrapping.[13,14] All models generated in this sequence having AIC values within 10% of the lowest value were considered as reasonable candidates. The final selection of a model was judged on model parsimony (the simpler the better), availability of the predictors (with respect to minimal resources and cost), and the attained sensitivity (with at least 50% specificity). All analyses were conducted using SAS 9.3 (Carey, NC, USA) and R 3.1.3 (Vienna, Austria; http://www.R-project.org). Additional models were created using the above process but with the absence of key variables used in deriving the primary model, including a model not including any variables likely to change over the course of admission. This was done to increase application in a variety of settings were certain variables may not be available.

Results

During the period of study 1822 subjects were screened for eligibility, of which 516 (28%) were excluded. Reasons for exclusion included isolated malnutrition (n=192), re-admission of previously enrolled subject (n=51), refusal of consent (n=22), cardiac disease (n=19), poisoning/drug reaction (n=19), cancer (n=12) as well as a plethora of other non-infectious admissions (n=165). One thousand three hundred and seven (1307) subjects admitted with a

presumed or proven infection were enrolled at the time of their admission. During the course of admission 64 (5.1%) subjects died, and 1242 (94.9%) were discharged alive (**Figure 1**). Among the children discharged 54% were male, and the median age was 18.1 months (IQR 10.8 – 34.6). Pneumonia, malaria and gastroenteritis were the most common clinical discharge diagnoses and were present in 31%, 50%, and 8% of discharged subjects respectively. According to anthropometric variables collected at admission, 30% of subjects were considered underweight (Weight for age z-score less than -2), 35% were considered wasted (weight for height/length z-score less than -2) and 29% were considered stunted (height/length for age z-score less than -2) (**Table 1**). Missing observations were minimal (**Table 2**).

Post-discharge mortality

The rate of successful follow-up during the post-discharge period was 98.3%, with only 6 subjects receiving no follow-up during this period. Overall, 61 (4.9%) children died following discharge. Of those that died, the median time to death was 30 days (IQR 7 – 81). Of the 61 deaths, 41 (67%) occurred outside of a hospital and 20 (33%) occurred during a hospital re-admission. Thirty variables were tested for univariate associations with post-discharge mortality (**Table 2**). Mid-upper arm circumference was the variable with the highest area under the receiver operating characteristic curve, 0.76 (95% CI 0.70 – 0.83) and was highly significant ($p < 0.0001$). Other anthropometric variables, including weight for age z-score, length/height for age z-score, and weight for length/height z-score were also highly associated with post-discharge mortality but had much lower areas under the ROC curve. Oxygen saturation was the most predictive of the non-anthropometric variables, with an area under the ROC curve of 0.65 (95% CI 0.57 – 0.73), followed by age and parasitemia with areas under the ROC curve of 0.64 (95% CI 0.56 – 0.70) and 0.60 (95% CI 0.55 – 0.65), respectively. Other variables achieving statistical

significance, but showing lower areas under the ROC curve included systolic blood pressure, axillary temperature, HIV status, abnormal Blantyre coma score (yes vs no), duration of illness prior to admission greater than 7 days and time since last hospitalization. Hemoglobin level, history of sibling deaths, maternal HIV status, maternal education and distance from admitting health facility were not associated with post-discharge mortality in the univariate analysis.

Multivariate prediction models

One primary model and three alternate models of equal sensitivity were developed for the prediction of six-month post discharge mortality (**Table 3**). Two alternate models were developed while systematically excluding oxygen saturation, and HIV status, respectively, since these may not be routinely available in all clinical settings. A fourth model was developed excluding variables most likely to change over the course of admission (i.e. clinical variables), giving the model utility for variables collected at any time throughout the hospital stay. The primary model included mid-upper arm circumference in mm (MUAC), oxygen saturation (SpO2) at admission (percent), time since previous hospitalization, the presence of abnormal Blantyre coma score (BCS) at admission, and HIV status. The area under the receiver operator characteristic curve was 0.82 (95% CI 0.76 – 0.87) (**Figure 2**). The model, at a cut-off of greater than 80% sensitivity, had a final sensitivity of 82% (95% CI 0.75 – 0.87) and a specificity of 66% (95% CI 64 – 69). In a population similar to this model derivation cohort we would expect the positive predictive value to be 11.1%, and the negative predictive value to be 98.6% (**Table 4)**. The final model equation for the primary model was: logit(p) = 7.71 + (-0.041; MUAC) + (-0.041; SpO2) + (-0.28; time period since last hospitalization) + (1.09; HIV positive) + (0.87; BCS <5).

Model two excluded oxygen saturation (**Table 3**). The final model included mid-upper arm circumference, time since last hospitalization, HIV status and the presence of an abnormal Blantyre coma score. The area under the ROC curve was 0.81 (95% CI 0.75 – 0.87). This model had a sensitivity of 80% (70 – 90) and specificity of 68% (95% CI 65 – 70) and would generate a positive and negative predictive value of 11.3% and 98.5%, respectively, in a population similar to the derivation cohort

The third model excluded HIV status (**Table 3**). This model had a final area under the ROC curve of 0.80 (95% CI 0.74 – 0.86) and a sensitivity of 80% (95%CI 70 – 90) and specificity of 63% (95% CI 60 – 66). The positive and negative predictive values were 10.2% and 98.4%, respectively.

The final model excluded all time changing clinical parameters (ex. Vital signs, SpO2, coma score etc.) so as to be applicable to data collected at any time during admission, including discharge. This model contained only three variables, MUAC, HIV status and the since the most recent hospitalization. This model achieved good performance characteristics including an AUC of 0.80 (95% CI 0.73 – 0.86). The sensitivity was specificity was 82% (95% CI 72 – 92) and the specificity was 61% (95% CI 59 – 64) and the positive and negative predictive values were 9.9% and 98.5%, respectively.

Discussion

This study represents the first systematic approach to the development of a simple risk-scoring algorithm for post-discharge mortality following admission for an acute infectious illness using prospectively collected data. The variables used in these models are easy to collect and include mid-upper arm circumference, oxygen saturation, Blantyre coma score, time since last

hospitalization, and HIV status. Four prediction models were developed to ensure its effective application in a variety of clinical circumstances. All four models had very similar performance characteristics with the most parsimonious model including only MUAC, HIV status and time since last hospitalization, with only marginally lower AUC than the full model with five variables. The models which were developed use only variables collected at admission and can therefore easily be incorporated into the discharge planning process during the hospital stay. Using these models, the identification of at-risk children would ensure that most children likely to die in the post-discharge period (about 80%) would be identified. These children have an average mortality risk of approximately over 10%, justifying the exploration of potentially life-saving interventions. Interventions found to be effective could likely be brought to scale without inordinately burdening already stressed health systems.

The development and implementation of predictive models into routine clinical care is not common in resource poor countries. The high prevalence of overlapping diseases (such as pneumonia, malaria and malnutrition), and the difficulty in creating reliable diagnostic algorithms to identify eligible populations, create significant difficulty in the application of disease specific models. To create models with uptake potential they would need to be linked with existing clinical practices and resources and would also require a shift in how infectious illness is viewed, not as an episodic diseases but as a continuum beyond the acute episode. The Integrated Management of Childhood Illness (IMCI), while not a predictive tool *per se*, is an algorithm-based approach for the diagnosis and management of acute infectious illnesses.[15] IMCI has seen significant uptake in many countries throughout Sub-Saharan Africa, and has provided a systematic approach to the care of children within health facilities. More importantly, it has been shown to improve care in the regions where it has been implemented.[16] However, the

IMCI does not address the important issue of post-discharge vulnerability and therefore fails to provide any guidance beyond the period of acute illness in the hospital, even though the post discharge period will claim as many lives as the acute hospital period. The integration of a post-discharge risk score into IMCI could begin to address this need.

This study is subject to several limitations. A primary limitation of this study is the relatively low number of outcomes observed. Although our initial sample size estimates were to observe 100 outcomes, we only observed 61. Our comprehensive follow-up of subjects ensured that missed outcomes are unlikely. Further, the performance of our model was good, with the lower limits of the calculated 95% confidence intervals for AUC, sensitivity and specificity remaining in an acceptable range. A further limitation is the lack of external validity. While our research sites represented the typical East African context, further research is required to ensure the validity of these models elsewhere, especially in areas with significant differences in the distribution of important diseases such as malaria, diarrhea and pneumonia and malnutrition. A limitation to application of the prediction models developed is that the risk score is based on a regression equation and cannot be easily computed without the assistance of a computer or similar device. However, with the increasing prevalence of mobile phones in developing countries, health interventions are increasingly focused on utilizing the computational power of mobile phones to implement life-saving technology. Several important health interventions use mobile technology to improve care.[17–19]

It is clear that malnutrition plays a major role in post-discharge mortality. Mid-upper arm circumference provided a significant proportion of the predictive power in our models, alone providing an AUC of 0.76, only 7% lower than the final full model. No models meeting our pre-specified criteria could be developed without the use of any anthropomorphic measure. The

importance of malnutrition has also been clearly demonstrated in other studies of post-discharge mortality.[20–22] Although first described over 50 years ago, environmental enteropathy (also called tropical enteropathy or environmental enteric dysfunction) has received significant attention in recent years. It has been suggested that changes in the gut microbiome and the small intestinal wall (flattened villi, inflammation and increased permeability) soon after birth can lead to early and irreversible stunting, frequent diarrheal illness and persistent systemic sub-clinical inflammation.[23–26] This appears to promote a vicious cycle of infection and malnutrition. While difficult to address, a focus on nutrition (micronutrient and macronutrient) before, during and following the acute phase of illness may reduce the exacerbation of this cycle. Half of the children who died during the course of this study did so more than 30 days following discharge. Therefore, emphasis must also be placed on preventing re-infection in vulnerable children. Promotion of good health behavior (including hygiene) during the post-discharge period is therefore likely to play an important role.

One further area for intervention is education on timely health seeking. Sixty-seven percent of the deaths in this study occurred outside of a hospital context, but 28% of the out-of hospital deaths occurred on the way to hospital. The education of mothers on the early warning signs of recurrent illness should also be emphasized during discharge since the common perception may be that recovery from infection brings a child back to a baseline level of risk, which is clearly not true. Since all children were enrolled during a hospital admission, physical inaccessibility was generally not an initial barrier. A previous study on the hospital burden of pediatric acute lower respiratory infections found that although 62% of children are treated in the hospital, 80% of deaths occur outside of the hospital.[27] While this study did not address the timing of the out-of-

hospital deaths in relation to the hospital visit, it is possible that many of these deaths occurred in the vulnerable months following discharge.

Conclusion

This study has derived a parsimonious risk-scoring tool for pediatric post-discharge mortality. Further work is required in external validation of this tool and the development of effective post-discharge interventions.

Figure 1 caption

Figure 1. Consort diagram of study flow

Figure 2 caption

Figure 2. Performance of the primary prediction model derived with data from admission. ROC = receiver operating characteristic. Sens = sensitivity. Spec = specificity. NPV = negative predictive value. PPV = positive predictive value.

Table 1. General Characteristics of discharged subjects (N=1242)

Characteristic	**Frequency**
Age < 12m	378 (30%)
Age 12m – 24m	379 (30%)
Age 24m – 36m	198 (16%)
Age 36m - 48m	150 (12%)
Age > 48m	138 (11%)
Male sex	682 (55%)
Length of stay < 3 days	487 (39%)
Length of stay 3 – 5 days	487 (39%)
Length of stay 6 – 10 days	173 (14%)
Length of stay > 10 days	96 (8%)
Discharge AMA	120 (10%)
Diagnoses	
Pneumonia	390 (31%)
Clinical malaria	621 (50%)
Parasitemia	418 (34%)
Gastroenteritis	96 (8%)
SSTI	7 (0.5%)
Meningitis	32 (2.5%)
Tuberculosis	17 (1.4%)
Measles	15 (1.2%)
Comorbidities	
HIV	58 (4.7%)
Sickle Cell	7 (0.5%)
Tuberculosis	21 (1.7%)
Admission Anthropometric Characteristics	
Underweight (WAZ <-2)	347 (30%)
Severe underweight (WAZ <-3)	188 (15%)
Wasting (WHZ <-2)	436 (35%)
Severe Wasting (WHZ <-3)	232 (17%)
Stunting (HAZ < -2)	357 (29%)
Severe Stunting (HAZ < -3)	187 (15%)
MUAC < 125	183 (15%)
MUAC < 115	96 (7.7%)

AMA = against medical advice; WAZ = weight for age z-score; WHZ = weight for height/length z-score; HAZ = height/length for age z-score; MUAC = mid-upper arm circumference

Table 2. Univariate analysis of potential predictor variables

Variable	Missing obs.	OR (95% CI)	AUC (95% CI)	P value
Male sex	0	0.90 (0.54 - 1.51)	0.51 (0.45 – 0.58)	0.700
Age (months)	3	0.97 (0.97 - 0.97)	0.64 (0.56 – 0.70)	0.003
MUAC (mm)	14	0.97 (0.96 - 0.98)	0.76 (0.70 – 0.83)	<0.001
Weight for age z-score	5	0.66 (0.57 - 0.76)	0.68 (0.60 – 0.76)	<0.001
Weight for length/height z-score	15	0.81 (0.72 - 0.91)	0.62 (0.55 – 0.70)	<0.001
Length/height for age z-score	16	0.79 (0.70 - 0.89)	0.63 (0.56 – 0.71)	<0.001
HR-age z-score	3	0.86 (0.74 - 0.99)	0.61 (0.53 – 0.69)	0.036
HR (raw)	0	1.00 (0.99 - 1.01)	0.53 (0.47 – 0.62)	0.728
RR-age z-score	3	0.99 (0.92 - 1.06)	0.53 (0.45 – 0.60)	0.747
RR (raw)	0	1.01 (1.00 - 1.03)	0.57 (0.50 – 0.63)	0.100
SBP z-score	21	0.94 (0.79 - 1.12)	0.50 (0.45 – 0.61)	0.526
SBP (raw)	6	0.98 (0.96 – 1.00)	0.58 (0.50 – 0.66)	0.018
DBP (raw)	6	0.99 (0.97 - 1.01)	0.55 (0.50 – 0.65)	0.255
Temperature (transformed)	0	1.02 (0.90 - 1.16)	0.51 (0.45 – 0.57)	0.789
Temperature (raw)	0	0.76 (0.62 - 0.93)	0.58 (0.50 – 0.65)	0.007
SpO2 (raw)	13	0.94 (0.92 - 0.96)	0.65 (0.57 – 0.73)	<0.001
SpO2 (transformed)	13	1.04 (1.02 - 1.05)	0.65 (0.57 – 0.73)	<0.001
HIV positive (vs neg.)	25	5.21 (2.55 - 10.65)	0.57 (0.52 – 0.62)	<0.001
Hemoglobin (g/dL)	10	0.95 (0.87 - 1.03)	0.56 (0.49 – 0.63)	0.227
Blantyre coma scale <5 (vs 5)	0	2.40 (1.27 - 4.57)	0.56 (0.50 – 0.61)	0.007
Positive blood smear (vs neg.)	11	0.33 (0.16 - 0.68)	0.60 (0.55 – 0.65)	0.002
Illness > 7 days prior to admission	1	0.50 (0.30 - 0.83)	0.58 (0.52 – 0.65)	0.008
Time since last hospitalization[§]	3	0.75 (0.62 – 0.90)	0.59 (0.52 – 0.67)	0.003
Sibling deaths	0	1.54 (0.89 - 2.65)	0.55 (0.48 – 0.61)	0.121
Number of children in family	2	1.02 (0.92 - 1.13)	0.50 (0.43 – 0.58)	0.750
Boil all drinking water	0	0.82 (0.47 - 1.42)	0.52 (0.46 – 0.58)	0.471
Maternal Age (years)	0	1.00 (0.97 - 1.04)	0.52 (0.41 – 0.57)	0.892
Maternal HIV (ref: neg.)				
HIV positive, n=142	0	1.79 (0.87 - 3.67)	0.54 (0.48 – 0.61)	0.113
HIV status unknown, n=220	0	1.27 (0.64 - 2.52)		0.499
Maternal Education (ref: < Primary 3)				
Primary 3 – Primary 7, n=630	0	1.18 (0.62 - 2.23)		0.619
Some Secondary, n=269	0	0.72 (0.31 - 1.70)	0.54 (0.50 – 0.63)	0.457
Post-secondary, n=93	0	1.18 (0.41 - 3.36)		0.762
Bednet use (ref = never)				
Sometimes	0	1.00 (0.48 - 2.09)	0.52 (0.45 – 0.59)	0.996
Always	0	0.85 (0.46 - 1.58)		0.612
Distance from hospital (ref: < 30 min.)				
30 to 60 minutes	0	0.71 (0.31 - 1.64)	0.56 (0.49 – 0.62)	0.421
More than 60 minutes	0	1.30 (0.70 - 2.41)		0.401

§ ordered as <7d, 7 – 30d, 30d – 1yr and never (analyzed as continuous)

MUAC = mid-upper arm circumference; HR = heart rate; RR= respiratory rate; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 3. Models developed for prediction of 6 month post-discharge mortality

Variable	Regression Estimate	p-value	OR (95% CI)
Model 1 – Primary model, Intercept = 7.7172			
MUAC	-0.0462	<0.0001	0.95 (0.94 – 0.97)
SpO2	-0.0411	0.0029	0.96 (0.93 – 0.99)
Time since last hosp.	-0.2775	0.0085	0.76 (0.62 – 0.93)
HIV positive	1.0915	0.0064	2.98 (1.36 – 6.53)
Abnormal BCS	0.8723	0.0150	2.39 (1.18 – 4.83)
Model 2 – Model without SpO2, Intercept = 4.4538			
MUAC	-0.0505	<0.0001	0.95 (0.94 – 9.97)
Time since last hosp.	-0.2503	0.0153	0.78 (0.64 – 0.95)
HIV positive	1.0902	0.0061	2.98 (1.37 – 6.48)
Abnormal BCS	1.0664	0.0022	2.91 (1.47 – 5.75)
Model 4 – Model without HIV, Intercept = 8.2813			
MUAC	-0.0492	<.0001	0.95 (0.94 – 0.97)
SpO2	-0.0412	0.0027	0.96 (0.93 – 0.99)
Time since last hosp.	-0.2870	0.0058	0.75 (0.61 – 0.92)
Abnormal BCS	0.8040	0.0248	2.23 (1.11 – 4.51)
Model 4 – Model without clinical variables, Intercept = 4.4511			
MUAC	-0.0492	<.0001	0.95 (0.94 – 0.97)
HIV positive	1.0143	0.0108	2.76 (1.26 – 6.01)
Time since last hosp.	-0.2458	0.0164	0.78 (0.64 – 0.96)

MUAC = mid-upper arm circumference; BCS = Blantyre coma score

Table 4. Model Characteristics at probability cut-offs ensuring model sensitivity of greater than 80%

Model	AUC (95% CI)	Prob. cut-off	Sens. (95% CI)	Spec. (95% CI)	PPV	NPV
1	0.82 (0.75 – 0.87)	0.035	82.0 (72.3 – 91.6)	66.2 (63.5 – 68.9)	11.1	98.6
2	0.81 (0.75 – 0.87)	0.040	80.3 (70.4 – 90.3)	67.5 (64.8 – 70.2)	11.3	98.5
3	0.80 (0.74 – 0.86)	0.031	80.3 (70.4 – 90.3)	63.4 (60.7 – 66.2)	10.2	98.4
4	0.80 (0.73 – 0.86)	0.035	82.0 (72.3 – 91.6)	61.4 (58.6 – 64.2)	9.9	98.5

AUC = area under the receiver operator characteristic curve; Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value

Acknowledgments: We gratefully acknowledge the contributions of Annet Twinomuguni, Justine Kamazima, Agaba Collins, Clare Komugisha, Solome Kobugyenyi, Alexander Mutungi and Hassan Bariahikwa. Without their dedication this study could not have been completed

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: This study was internally funded. M Wiens was supported by a fellowship from the Canadian Institutes of Health Research, the Michael Smith Foundation for Health research and the Canadian Child Health Clinician Scientist Program.

Contributor Statement

Design: MO Wiens, E Kumbakumba, CP Larson, JM Ansermino, J Singer, H Wong, A Ndamira, J Kabakyenga, N Kissoon, J Kiwanuka

Data Collection: MO Wiens, E Kumbakumba, JM Ansermino

Analysis: MO Wiens, Analysis, J Singer, H Wong, G Zhou

Drafting of initial manuscript: MO Wiens

Reviewing and revising manuscript: MO Wiens, E Kumbakumba, CP Larson, JM Ansermino, J Singer, N Kissoon, H Wong, A Ndamira, J Kabakyenga, G Zhou, J Kiwanuka

Approval of final manuscript: All Authors

Data Sharing: No additional data available

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430–40.

2. Wang H, Liddell C a, Coates MM, Mooney MD, Levitz CE, Schumacher AE, et al. Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;957–79.

3. Wiens M, Pawluk S, Kissoon N. Pediatric Post-Discharge Mortality in Resource Poor Countries: A Systematic Review. PLoS One [Internet]. 2013 Jan [cited 2014 Jun 19];8(6):e66698.

4. Karlen W, Dumont G, Petersen C, Gow J, Lim J, Sleiman J, et al. Human-centered phone oximeter interface design for the operating room: Pulse Oximeter Interfaced to a Mobile Device for Anesthesia Monitoring in the Developing World. Proceedings of the International Conference on Health Informatics. Rome, Italy: SciTePress; 2011. p. 433–8.

5. The WHO Child Growth Standards [Internet]. 2006 [cited 2015 Mar 1]. Available from: http://www.who.int/childgrowth/standards/en/

6. Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, MacOnochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: A systematic review of observational studies. Lancet. 2011;377(9770):1011–8.

7. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114:555–76.

8. National Implementation Guidelines for HIV Counselling and Testing in Uganda [Internet]. Kampala, Uganda; 2010. Available from: http://library.health.go.ug/publications

9. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.

10. Wiens MO, Kissoon N, Kumbakumba E, Singer J, Moschovis P, Ansermino JM, et al. Selecting candidate predictor variables for the modelling of post-discharge mortality: A protocol development project. Submitted. 2015.

11. Hosmer DW, Lemeshow S. Goodness of fit tests for the multiple logistic regression model. Commun Stat - Theory Methods. 1980;9(10):1043–69.

12. Van Buuren S, Groothuis-Oudshoorn K. Multivariate Imputation by Chained Equations. J Stat Softw. 2011;45(3):1–67.

13. Stone M. An Asymptotic Equivalence of Choice of Model by Cross-Validation and Akaike's Criterion. J R Stat Soc Ser B-Methodological. 1977;39(1):44–7.

14. Shibata R. Bootstrap estimate of Kullback-Leibler information for model selection. Stat Sin. 1997;7:375–94.

15. World Health Organization. Integrated Management of Childhood Illness: distance learning course. Geneva: World Health Organization; 2014.

16. Nguyen DTK, Leung KK, McIntyre L, Ghali W a., Sauve R. Does Integrated Management of Childhood Illness (IMCI) Training Improve the Skills of Health Workers? A Systematic Review and Meta-Analysis. PLoS One. 2013;8(6).

17. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet [Internet]. Elsevier Ltd; 2010;376(9755):1838–45.

18. Obasola OI, Mabawonku I, Lagunju I. A Review of e-Health Interventions for Maternal and Child Health in Sub-Sahara Africa. Matern Child Health J. 2015;In press. Available from: http://link.springer.com/10.1007/s10995-015-1695-0

19. Mitchell M, Hedt-Gauthier BL, Msellemu D, Nkaka M, Lesh N. Using electronic technology to improve clinical care - results from a before-after cluster trial to evaluate assessment and classification of sick children according to Integrated Management of Childhood Illness (IMCI) protocol in Tanzania. BMC Med Inform Decis Mak. BMC Medical Informatics and Decision Making; 2013;13(1):95.

20. Moïsi JC, Gatakaa H, Berkley JA, Maitland K, Mturi N, Newton CR, et al. Excess child mortality after discharge from hospital in Kilifi, Kenya: a retrospective cohort analysis. Bull World Health Organ. 2011;89(10):725–32.

21. Islam MA, Rahman MM, Mahalanabis D, Rahman a K. Death in a diarrhoeal cohort of infants and young children soon after discharge from hospital: risk factors and causes by verbal autopsy. J Trop Pediatr. 1996 Dec;42(6):342–7.

22. West TE, Goetghebuer T, Milligan P, Mulholland EK, Weber MW. Long-term morbidity and mortality following hypoxaemic lower respiratory tract infection in Gambian children. Bull World Health Organ. 1999 Jan;77(2):144–8.

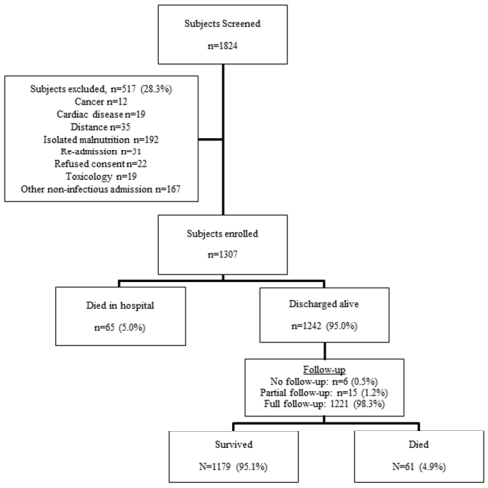
23. Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. Am J Trop Med Hyg. 2012;86(5):756–63.

24. Keusch GT, Denno DM, Black RE, Duggan C, Guerrant RL, Lavery J V, et al. Environmental Enteric Dysfunction: Pathogenesis, Diagnosis, and Clinical Consequences. Clin Infect Dis. 2014;59(Suppl 4):207–12.

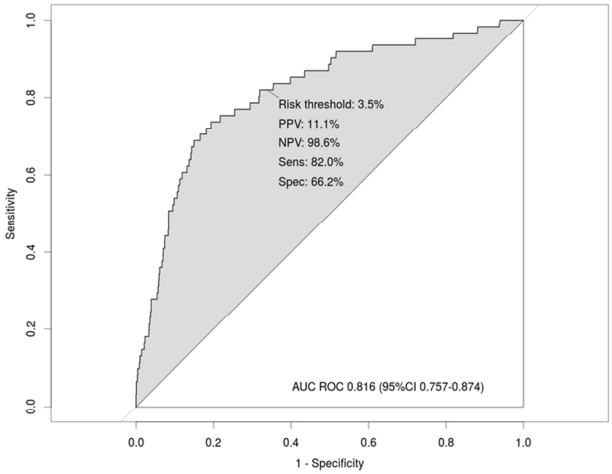
25. Kosek M, Guerrant RL, Kang G, Yori PP, Gratz J, Gottlieb M, et al. Assessment of Environmental Enteropathy in the MAL-ED Cohort Study: Theoretical and Analytic Framework. Clin Infect Dis. 2014;59(Suppl 4):239–47.

26. Jones KD, Thitiri J, Ngari M, Berkley JA. Childhood malnutrition: Toward an understanding of infections, inflammation, and antimicrobials. Food Nutr Bull. 2014;35(2):64–70.

27. Nair H, Simões E a F, Rudan I, Gessner BD, Azziz-Baumgartner E, Zhang JSF, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet. 2013 Apr 20;381(9875):1380–90.



338x190mm (96 x 96 DPI)



338x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			10

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	11/12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11/12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11/12
		(*b*) Report category boundaries when continuous variables were categorized	11/12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			13
Key results	18	Summarise key results with reference to study objectives	13
Limitations			15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Post-Discharge Mortality in Children with Acute Infectious Diseases: Derivation of Post-Discharge Mortality Prediction Models

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009449.R2
Article Type:	Research
Date Submitted by the Author:	16-Oct-2015
Complete List of Authors:	Wiens, Matthew; University of British Columbia, School of Population and Public Health Kumbakumba, Elias; Mbarara University of Science and Technology, Department of Pediatrics Larson, Charles P ; University of British Columbia, Department of Pediatrics/Centre for International Child Health, BC Children's Hospital Ansermino, Mark; University of British Columbia, Department of Pediatric Anesthesia Singer, Joel; University of British Columbia, School of Population and Public Health Kissoon, Niranjan; University of British Columbia, Department of Pediatrics Wong, Hubert; University of British Columbia, School of Population and Public Health Ndamira, Andrew; Mbarara University of Science and Technology, Department of Pediatarics Kabakyenga, Jerome; Mbarara University of Science and Technology, Maternal, Newborn and Child health Institute Kiwanuka, Julius; Mbarara University of Science and Technology, Department of Pediatarics Zhou, Guohai; University of British Columbia, Department of Statistics
Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Infectious diseases, Paediatrics
Keywords:	PAEDIATRICS, EPIDEMIOLOGY, Paediatric infectious disease & immunisation < PAEDIATRICS

Post-Discharge Mortality in Children with Acute Infectious Diseases: Derivation of Post-Discharge Mortality Prediction Models

MO Wiens[1], E Kumbakumba[2], CP Larson[3], JM Ansermino[4], J Singer[1,6], N Kissoon[5], H Wong[1], A Ndamira[2], J Kabakyenga[7], J Kiwanuka[2], G Zhou[8]

1. School of Population and Public Health, University of British Columbia, Vancouver, Canada
2. Department of Pediatrics, Mbarara University of Science and Technology, Mbarara, Uganda
3. Center for International Child Health, BC Children's Hospital, Child and Family Research Institute, Vancouver Canada
4. Department of Pediatric Anesthesiology, BC Children's Hospital and University of British Columbia, Vancouver, Canada
5. Department of Pediatrics, BC Children's Hospital and University of British Columbia, Vancouver, Canada
6. Canadian HIV Trials Network, St. Paul's Hospital and University of British Columbia, Vancouver, Canada
7. Maternal, Newborn and Child Health Institute, Mbarara University of Science and Technology, Mbarara, Uganda
8. Department of statistics, University of British Columbia, Vancouver, Canada

Word count: 3344

Correspondence to:

Matthew Wiens, PharmD PhD
School of Population and Public Health
University of British Columbia
Vancouver, Canada
mowiens@outlook.com

Abstract

Objectives: To derive a model of paediatric post-discharge mortality following acute infectious illness.

Design: Prospective cohort study

Setting: Two hospitals in South-western Uganda.

Participants: 1307 children 6 months and 5 years admitted with a proven or suspected infection. 1242 children were discharged alive and follow-up 6 months following discharge. The six-month follow-up rate was 98.3%.

Interventions: None.

Primary and secondary outcome measures: The primary outcome was post-discharge mortality within 6 months following the initial hospital discharge

Results: 64 children died during admission (5.0%) and 61 died within six month of discharge (4.9%). Of those that died following discharge, 31 (51%) occurred within the first 30 days. The final adjusted model for the prediction of post-discharge mortality included the variables mid-upper arm circumference (OR: 0.95, 95% CI: 0.94–0.97, per 1 mm increase), time since last hospitalization (OR: 0.76, 95% CI: 0.61 – 0.93, for each increased period of no hospitalization), oxygen saturation (OR: 0.96, 95% CI: 0.93 – 0·99, per 1% increase), abnormal Blantyre coma score (OR: 2.39, 95% CI: 1·18 –4.83), and HIV positive status (OR: 2.98, 95% CI: 1.36 – 6.53). This model produced a receiver operating characteristic curve with an AUC of 0.82. With sensitivity of 80%, our model had a specificity of 66%. Approximately 35% of children would be identified as high risk (11.1% mortality risk) and the remaining would be classified as low risk (1.4% mortality risk), in a similar cohort.

Conclusions: Mortality following discharge is a poorly recognised contributor to child mortality. Identification of at-risk children is critical in developing post-discharge interventions. A simple prediction tool that uses five easily collected variables can be used to identify children at high risk of death after discharge. Improved discharge planning and care could be provided for high risk children.

Strengths and limitations of this study

The primary strengths of this study are (1) prospective and rigorous data collection and (2) near complete follow-up.

Further strengths include the derivation of multiple similar models to allow prediction in circumstances where not all variables may be available

Regression models can easily be incorporated into a mobile-health based tool for simple and rapid prediction by health workers

The primary limitations of this study are (1) relatively few outcomes and (2) lack of external validity. Despite few outcomes our models performed quite well.

These limitations highlight the need for further research on this important but neglected topic.

The identification of high risk does not imply that risk can be reduced. Further work is needed on the development of post-discharge interventions to reduce this burden.

Background

Acute infectious diseases continue to be the most important contributor to the six million children younger than five years who die every year, particularly in Africa.[1] It is widely accepted that as a global community we have fallen short in reducing under-five mortality, as demonstrated by the fact that most developing countries, especially those in sub-Saharan Africa will not achieve the fourth millennium development goal of a two-thirds reduction in child mortality.[2] An important but neglected contributor to infectious disease related mortality is the vulnerable period following hospital discharge.

A recent systematic review of pediatric studies assessing post-discharge mortality in resource poor countries and found that post-discharge mortality often exceed in-hospital mortality.[3] Thus attention to at-risk populations post discharge is sorely needed. However, while several factors were consistently found to be associated with mortality following discharge, including malnutrition, HIV and severe pneumonia, easy identification is essential in order to develop targeted post-discharge interventions. Ideally, the unacceptably high risk of morbidity and mortality following discharge suggests that all children should be afforded follow up care. However, significant resource constraints in the countries most affected by this issue preclude any significant intervention on all discharged children. Therefore, the ability to quickly and effectively identify at-risk children would be an invaluable step towards the implementation of life-saving post-discharge interventions. An important and easily identified dichotomy among hospital admissions are infectious diseases and non-infectious disease related admissions, such as trauma, cancer and congenital diseases. Although further divisions based on etiology of infection, or an underlying risk factor such as malnutrition or HIV status, may be an attractive approach in risk stratification, significant difficulties in disease definitions and often overlapping

risks makes this approach very difficult. The development of a robust yet simple risk-scoring algorithm could significantly advance a systematic and evidence based approach in post-discharge care.

The purpose of this study was to derive simple prediction models that could efficiently stratify children according to post-discharge mortality risk.

Methods

Population

Mbarara, a city of approximately 195,000, is the largest city in the Southwestern region of Uganda. This study was conducted at two hospitals in Mbarara. The Mbarara Regional Referral Hospital (MRRH) is the main referral hospital in Southwestern Uganda. It is a public hospital funded by the Uganda Ministry of Health. MRRH is associated with the Mbarara University of Science and Technology and is a primary training site for its health care graduates. The pediatric ward admits approximately 5000 patients per year. The Holy Innocents Children's Hospital (HICH) is a faith-based children's hospital offering subsidized fee-for-service outpatient and in-patient care in Mbarara. The HICH admits approximately 2500 patients per year.

This was a prospective observational study conducted between March 2012 and December 2013. This study was approved the institutional review boards at the University of British Columbia (Canada) and the Mbarara University of Science and Technology (Uganda) as well as the Uganda National Council for Science and Technology and Office of the President. This study was voluntary and written informed consent was provided by a parent or guardian of all children who were enrolled.

Eligibility

All children aged 6 months to five years who were admitted with a proven or suspected infection were eligible for enrollment. The upper age limit was chosen to coincide with the under-five target group of the millennium development goals. The lower age limit was chosen for logistic (census enrollment with limited research staff) and statistical considerations (group homogeneity). Subjects already enrolled in the study were not eligible to be enrolled during subsequent admissions.

Study procedure

Following enrollment, a research nurse obtained and recorded clinical signs including a one minute respiratory rate, blood pressure (automated), axillary temperature, Blantyre coma score, and using the Phone Oximeter [4], one mininute photoplethysmogram (PPG), blood oxygen saturation (SpO_2) and heart rate. Anthropometric data (height, weight, mid-upper arm circumference) were also measured and recorded. Age-dependent demographic variables collected at enrollment were converted to age corrected z-scores according to the World Health Organization Child Growth Standards.[5] The age corrected heart rate and respiratory rate z-scores were obtained by standardizing the raw measurements using the median and SD values provided by Fleming et al.[6] The age corrected z-scores for systolic blood pressure were calculated using subjects' height, according to the procedures previously described.[7]

A blood sample was taken for measurement of hemoglobin, HIV and a malaria blood smear (microscopy). HIV status was determined using the national rapid diagnostic test serial algorithm.[8] All positive tests on the Determine Antibody Test were confirmed by a separate test

(UniGold). Children under 12 months of age with a positive test were confirmed using PCR. Hemoglobin was measured on a Beckman Coulter Ac.T Hematology analyzer.

An interview was conducted with the subject's parent/guardian and information about previous admissions, distance from health facility, transportation costs, bed-net use, maternal education, maternal age, maternal HIV status, history of sibling deaths and drinking water safety were elicited. Subjects received routine care during their hospital stay and were discharged at the discretion of the treating medical team. The discharge status of all enrolled subjects was recorded as death, referral, discharged alive, and discharged against medical advice. The diagnoses made by the medical team were also recorded. Upon discharge, families with active telephone lines were contacted at months two and four to determine the vital status of the child. Families with no telephone access received in-person follow-up by a field officer. At approximately six months following discharge all subjects received in-person follow-up. In addition to post-discharge vital status, health seeking and re-hospitalizations since the initial discharge were also recorded.

Study data were collected and managed using REDCap electronic data capture tools hosted at the Child and Family Research Institute, Vancouver, Canada.[9] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Candidate predictor variables were derived using a two-round modified Delphi approach. Briefly, 23 experts in relevant disciplines were solicited to complete an online survey and

provide feedback on an initial list of proposed predictors. Predictors were evaluated on considerations of utility as predictors, availability, cost and resource related applicability. Experts were asked to provide additional potential variables which were then evaluated during a second round of surveys. Data was evaluated by the research team and a final list of candidate predictor variables for modelling was determined.[10]

Outcomes

The primary outcome was post-discharge mortality at any time during the six month post-discharge period.

Sample size

For the derivation of prediction models, standard calculations of sample size do not apply since these calculations do not account for the model development process (i.e., selection of variables and the optimization to achieve specified sensitivity and specificity cut-offs). For this study we determined the sample size needed to validate the derived model and plan to use an equal number of patients for the derivation phase. For the validation study, assuming that the derived model achieves a sensitivity of 85% with at least 50% specificity, 100 events, corresponding to a total sample of approximately 1000 live-discharges (assuming a post-discharge mortality rate of 10%), would be needed to obtain 80% power for ensuring that the lower 95% confidence limit on sensitivity will be at least 75%. Since resources are scarce, a higher sensitivity at the expense of specificity would further limit practical application of such a model. An interim analysis of the study showed that the post-discharge mortality rate would likely not exceed 5% and enrollment was stopped when 1307 subjects were enrolled.

Statistical Analysis

All variables were assessed using univariate logistic regression to determine their level of association with the primary outcome. Continuous variables were assessed for model fit using the Hosmer-Lemeshow test.[11] Missing data was imputed by the method of multivariate imputation by chained equations.[12] Following univariate analysis candidate models were generated using a step-wise selection procedure minimizing Akaike's Information Criterion (AIC). This method is considered asymptotically equivalent to cross-validation and bootstrapping.[13,14] All models generated in this sequence having AIC values within 10% of the lowest value were considered as reasonable candidates. The final selection of a model was judged on model parsimony (the simpler the better), availability of the predictors (with respect to minimal resources and cost), and the attained sensitivity (with at least 50% specificity). All analyses were conducted using SAS 9.3 (Carey, NC, USA) and R 3.1.3 (Vienna, Austria; http://www.R-project.org). Additional models were created using the above process but with the absence of key variables used in deriving the primary model, including a model not including any variables likely to change over the course of admission. This was done to increase application in a variety of settings were certain variables may not be available.

Results

During the period of study 1822 subjects were screened for eligibility, of which 516 (28%) were excluded. Reasons for exclusion included isolated malnutrition (n=192), re-admission of previously enrolled subject (n=51), refusal of consent (n=22), cardiac disease (n=19), poisoning/drug reaction (n=19), cancer (n=12) as well as a plethora of other non-infectious admissions (n=165). One thousand three hundred and seven (1307) subjects admitted with a

presumed or proven infection were enrolled at the time of their admission. During the course of admission 64 (5.1%) subjects died, and 1242 (94.9%) were discharged alive (**Figure 1**). Among the children discharged 54% were male, and the median age was 18.1 months (IQR 10.8 – 34.6). Pneumonia, malaria and gastroenteritis were the most common clinical discharge diagnoses and were present in 31%, 50%, and 8% of discharged subjects respectively. According to anthropometric variables collected at admission, 30% of subjects were considered underweight (Weight for age z-score less than -2), 35% were considered wasted (weight for height/length z-score less than -2) and 29% were considered stunted (height/length for age z-score less than -2) (**Table 1**). Missing observations were minimal (**Table 2**).

Post-discharge mortality

The rate of successful follow-up during the post-discharge period was 98.3%, with only 6 subjects receiving no follow-up during this period. Overall, 61 (4.9%) children died following discharge. Of those that died, the median time to death was 30 days (IQR 7 – 81). Of the 61 deaths, 41 (67%) occurred outside of a hospital and 20 (33%) occurred during a hospital re-admission. Thirty variables were tested for univariate associations with post-discharge mortality (**Table 2**). Mid-upper arm circumference was the variable with the highest area under the receiver operating characteristic curve, 0.76 (95% CI 0.70 – 0.83) and was highly significant ($p < 0.0001$). Other anthropometric variables, including weight for age z-score, length/height for age z-score, and weight for length/height z-score were also highly associated with post-discharge mortality but had much lower areas under the ROC curve. Oxygen saturation was the most predictive of the non-anthropometric variables, with an area under the ROC curve of 0.65 (95% CI 0.57 – 0.73), followed by age and parasitemia with areas under the ROC curve of 0.64 (95% CI 0.56 – 0.70) and 0.60 (95% CI 0.55 – 0.65), respectively. Other variables achieving statistical

significance, but showing lower areas under the ROC curve included systolic blood pressure, axillary temperature, HIV status, abnormal Blantyre coma score (yes vs no), duration of illness prior to admission greater than 7 days and time since last hospitalization (analyzed as continuous variable and ordered as <7d, 7-30d, 30d – 1yr, >1yr and never). Hemoglobin level, history of sibling deaths, maternal HIV status, maternal education and distance from admitting health facility were not associated with post-discharge mortality in the univariate analysis.

Multivariate prediction models

One primary model and three alternate models of equal sensitivity were developed for the prediction of six-month post discharge mortality (**Table 3**). Two alternate models were developed while systematically excluding oxygen saturation, and HIV status, respectively, since these may not be routinely available in all clinical settings. A fourth model was developed excluding variables most likely to change over the course of admission (i.e. clinical variables), giving the model utility for variables collected at any time throughout the hospital stay. The primary model included mid-upper arm circumference in mm (MUAC), oxygen saturation (SpO2) at admission (percent), time since previous hospitalization, the presence of abnormal Blantyre coma score (BCS) at admission, and HIV status. The area under the receiver operator characteristic curve was 0.82 (95% CI 0.76 – 0.87) (**Figure 2**). The model, at a cut-off of greater than 80% sensitivity, had a final sensitivity of 82% (95% CI 0.75 – 0.87) and a specificity of 66% (95% CI 64 – 69). In a population similar to this model derivation cohort we would expect the positive predictive value to be 11.1%, and the negative predictive value to be 98.6% (**Table 4)**. The final model equation for the primary model was: logit(p) = 7.71 + (-0.041; MUAC) + (-0.041; SpO2) + (-0.28; time period since last hospitalization) + (1.09; HIV positive) + (0.87; BCS <5).

Model two excluded oxygen saturation (**Table 3**). The final model included mid-upper arm circumference, time since last hospitalization, HIV status and the presence of an abnormal Blantyre coma score. The area under the ROC curve was 0.81 (95% CI 0.75 – 0.87). This model had a sensitivity of 80% (70 – 90) and specificity of 68% (95% CI 65 – 70) and would generate a positive and negative predictive value of 11.3% and 98.5%, respectively, in a population similar to the derivation cohort

The third model excluded HIV status (**Table 3**). This model had a final area under the ROC curve of 0.80 (95% CI 0.74 – 0.86) and a sensitivity of 80% (95%CI 70 – 90) and specificity of 63% (95% CI 60 – 66). The positive and negative predictive values were 10.2% and 98.4%, respectively.

The final model excluded all time changing clinical parameters (ex. Vital signs, SpO2, coma score etc.) so as to be applicable to data collected at any time during admission, including discharge. This model contained only three variables, MUAC, HIV status and the since the most recent hospitalization. This model achieved good performance characteristics including an AUC of 0.80 (95% CI 0.73 – 0.86). The sensitivity was specificity was 82% (95% CI 72 – 92) and the specificity was 61% (95% CI 59 – 64) and the positive and negative predictive values were 9.9% and 98.5%, respectively.

Discussion

This study represents the first systematic approach to the development of a simple risk-scoring algorithm for post-discharge mortality following admission for an acute infectious illness using prospectively collected data. The variables used in these models are easy to collect and include mid-upper arm circumference, oxygen saturation, Blantyre coma score, time since last

hospitalization, and HIV status. Four prediction models were developed to ensure its effective application in a variety of clinical circumstances. All four models had very similar performance characteristics with the most parsimonious model including only MUAC, HIV status and time since last hospitalization, with only marginally lower AUC than the full model with five variables. The models which were developed use only variables collected at admission and can therefore easily be incorporated into the discharge planning process during the hospital stay. Using these models, the identification of at-risk children would ensure that most children likely to die in the post-discharge period (about 80%) would be identified. These children have an average mortality risk of approximately over 10%, justifying the exploration of potentially life-saving interventions. Interventions found to be effective could likely be brought to scale without inordinately burdening already stressed health systems.

The development and implementation of predictive models into routine clinical care is not common in resource poor countries. The high prevalence of overlapping diseases (such as pneumonia, malaria and malnutrition), and the difficulty in creating reliable diagnostic algorithms to identify eligible populations, create significant difficulty in the application of disease specific models. To create models with uptake potential they would need to be linked with existing clinical practices and resources and would also require a shift in how infectious illness is viewed, not as an episodic diseases but as a continuum beyond the acute episode. The Integrated Management of Childhood Illness (IMCI), while not a predictive tool *per se*, is an algorithm-based approach for the diagnosis and management of acute infectious illnesses.[15] IMCI has seen significant uptake in many countries throughout Sub-Saharan Africa, and has provided a systematic approach to the care of children within health facilities. More importantly, it has been shown to improve care in the regions where it has been implemented.[16] However, the

IMCI does not address the important issue of post-discharge vulnerability and therefore fails to provide any guidance beyond the period of acute illness in the hospital, even though the post discharge period will claim as many lives as the acute hospital period. The integration of a post-discharge risk score into IMCI could begin to address this need.

This study is subject to several limitations. A primary limitation of this study is the relatively low number of outcomes observed. Although our initial sample size estimates were to observe 100 outcomes, we only observed 61. Our comprehensive follow-up of subjects ensured that missed outcomes are unlikely. Further, the performance of our model was good, with the lower limits of the calculated 95% confidence intervals for AUC, sensitivity and specificity remaining in an acceptable range. A further limitation is the lack of external validity. While our research sites represented the typical East African context, further research is required to ensure the validity of these models elsewhere, especially in areas with significant differences in the distribution of important diseases such as malaria, diarrhea and pneumonia and malnutrition. A limitation to application of the prediction models developed is that the risk score is based on a regression equation and cannot be easily computed without the assistance of a computer or similar device. However, with the increasing prevalence of mobile phones in developing countries, health interventions are increasingly focused on utilizing the computational power of mobile phones to implement life-saving technology. Several important health interventions use mobile technology to improve care.[17–19]

It is clear that malnutrition plays a major role in post-discharge mortality. Mid-upper arm circumference provided a significant proportion of the predictive power in our models, alone providing an AUC of 0.76, only 7% lower than the final full model. No models meeting our pre-specified criteria could be developed without the use of any anthropomorphic measure. The

importance of malnutrition has also been clearly demonstrated in other studies of post-discharge mortality.[20–22] Although first described over 50 years ago, environmental enteropathy (also called tropical enteropathy or environmental enteric dysfunction) has received significant attention in recent years. It has been suggested that changes in the gut microbiome and the small intestinal wall (flattened villi, inflammation and increased permeability) soon after birth can lead to early and irreversible stunting, frequent diarrheal illness and persistent systemic sub-clinical inflammation.[23–26] This appears to promote a vicious cycle of infection and malnutrition. While difficult to address, a focus on nutrition (micronutrient and macronutrient) before, during and following the acute phase of illness may reduce the exacerbation of this cycle. Half of the children who died during the course of this study did so more than 30 days following discharge. Therefore, emphasis must also be placed on preventing re-infection in vulnerable children. Promotion of good health behavior (including hygiene) during the post-discharge period is therefore likely to play an important role.

One further area for intervention is education on timely health seeking. Sixty-seven percent of the deaths in this study occurred outside of a hospital context, but 28% of the out-of hospital deaths occurred on the way to hospital. The education of mothers on the early warning signs of recurrent illness should also be emphasized during discharge since the common perception may be that recovery from infection brings a child back to a baseline level of risk, which is clearly not true. Since all children were enrolled during a hospital admission, physical inaccessibility was generally not an initial barrier. A previous study on the hospital burden of pediatric acute lower respiratory infections found that although 62% of children are treated in the hospital, 80% of deaths occur outside of the hospital.[27] While this study did not address the timing of the out-of-

hospital deaths in relation to the hospital visit, it is possible that many of these deaths occurred in the vulnerable months following discharge.

Conclusion

This study has derived a parsimonious risk-scoring tool for pediatric post-discharge mortality. Further work is required in external validation of this tool and the development of effective post-discharge interventions.

Figure 1 caption

Figure 1. Consort diagram of study flow

Figure 2 caption

Figure 2. Performance of the primary prediction model derived with data from admission. ROC = receiver operating characteristic. Sens = sensitivity. Spec = specificity. NPV = negative predictive value. PPV = positive predictive value.

Table 1. General Characteristics of discharged subjects (N=1242)

Characteristic	**Frequency**
Age < 12m	378 (30%)
Age 12m – 24m	379 (30%)
Age 24m – 36m	198 (16%)
Age 36m - 48m	150 (12%)
Age > 48m	138 (11%)
Male sex	682 (55%)
Length of stay < 3 days	487 (39%)
Length of stay 3 – 5 days	487 (39%)
Length of stay 6 – 10 days	173 (14%)
Length of stay > 10 days	96 (8%)
Discharge AMA	120 (10%)
Diagnoses	
Pneumonia	390 (31%)
Clinical malaria	621 (50%)
Parasitemia	418 (34%)
Gastroenteritis	96 (8%)
SSTI	7 (0.5%)
Meningitis	32 (2.5%)
Tuberculosis	17 (1.4%)
Measles	15 (1.2%)
Comorbidities	
HIV	58 (4.7%)
Sickle Cell	7 (0.5%)
Tuberculosis	21 (1.7%)
Admission Anthropometric Characteristics	
Underweight (WAZ <-2)	347 (30%)
Severe underweight (WAZ <-3)	188 (15%)
Wasting (WHZ <-2)	436 (35%)
Severe Wasting (WHZ <-3)	232 (17%)
Stunting (HAZ < -2)	357 (29%)
Severe Stunting (HAZ < -3)	187 (15%)
MUAC < 125	183 (15%)
MUAC < 115	96 (7.7%)

AMA = against medical advice; WAZ = weight for age z-score; WHZ = weight for height/length z-score; HAZ = height/length for age z-score; MUAC = mid-upper arm circumference

Table 2. Univariate analysis of potential predictor variables

Variable	Missing obs.	OR (95% CI)	AUC (95% CI)	P value
Male sex	0	0.90 (0.54 - 1.51)	0.51 (0.45 – 0.58)	0.700
Age (months)	3	0.97 (0.97 - 0.97)	0.64 (0.56 – 0.70)	0.003
MUAC (mm)	14	0.97 (0.96 - 0.98)	0.76 (0.70 – 0.83)	<0.001
Weight for age z-score	5	0.66 (0.57 - 0.76)	0.68 (0.60 – 0.76)	<0.001
Weight for length/height z-score	15	0.81 (0.72 - 0.91)	0.62 (0.55 – 0.70)	<0.001
Length/height for age z-score	16	0.79 (0.70 - 0.89)	0.63 (0.56 – 0.71)	<0.001
HR-age z-score	3	0.86 (0.74 - 0.99)	0.61 (0.53 – 0.69)	0.036
HR (raw)	0	1.00 (0.99 - 1.01)	0.53 (0.47 – 0.62)	0.728
RR-age z-score	3	0.99 (0.92 - 1.06)	0.53 (0.45 – 0.60)	0.747
RR (raw)	0	1.01 (1.00 - 1.03)	0.57 (0.50 – 0.63)	0.100
SBP z-score	21	0.94 (0.79 - 1.12)	0.50 (0.45 – 0.61)	0.526
SBP (raw)	6	0.98 (0.96 – 1.00)	0.58 (0.50 – 0.66)	0.018
DBP (raw)	6	0.99 (0.97 - 1.01)	0.55 (0.50 – 0.65)	0.255
Temperature (transformed)	0	1.02 (0.90 - 1.16)	0.51 (0.45 – 0.57)	0.789
Temperature (raw)	0	0.76 (0.62 - 0.93)	0.58 (0.50 – 0.65)	0.007
SpO2 (raw)	13	0.94 (0.92 - 0.96)	0.65 (0.57 – 0.73)	<0.001
SpO2 (transformed)	13	1.04 (1.02 - 1.05)	0.65 (0.57 – 0.73)	<0.001
HIV positive (vs neg.)	25	5.21 (2.55 - 10.65)	0.57 (0.52 – 0.62)	<0.001
Hemoglobin (g/dL)	10	0.95 (0.87 - 1.03)	0.56 (0.49 – 0.63)	0.227
Blantyre coma scale <5 (vs 5)	0	2.40 (1.27 - 4.57)	0.56 (0.50 – 0.61)	0.007
Positive blood smear (vs neg.)	11	0.33 (0.16 - 0.68)	0.60 (0.55 – 0.65)	0.002
Illness > 7 days prior to admission	1	0.50 (0.30 - 0.83)	0.58 (0.52 – 0.65)	0.008
Time since last hospitalization[§]	3	0.75 (0.62 – 0.90)	0.59 (0.52 – 0.67)	0.003
Sibling deaths	0	1.54 (0.89 - 2.65)	0.55 (0.48 – 0.61)	0.121
Number of children in family	2	1.02 (0.92 - 1.13)	0.50 (0.43 – 0.58)	0.750
Boil all drinking water	0	0.82 (0.47 - 1.42)	0.52 (0.46 – 0.58)	0.471
Maternal Age (years)	0	1.00 (0.97 - 1.04)	0.52 (0.41 – 0.57)	0.892
Maternal HIV (ref: neg.)				
HIV positive, n=142	0	1.79 (0.87 - 3.67)	0.54 (0.48 – 0.61)	0.113
HIV status unknown, n=220	0	1.27 (0.64 - 2.52)		0.499
Maternal Education (ref: < Primary 3)				
Primary 3 – Primary 7, n=630	0	1.18 (0.62 - 2.23)		0.619
Some Secondary, n=269	0	0.72 (0.31 - 1.70)	0.54 (0.50 – 0.63)	0.457
Post-secondary, n=93	0	1.18 (0.41 - 3.36)		0.762
Bednet use (ref = never)				
Sometimes	0	1.00 (0.48 - 2.09)	0.52 (0.45 – 0.59)	0.996
Always	0	0.85 (0.46 - 1.58)		0.612
Distance from hospital (ref: < 30 min.)				
30 to 60 minutes	0	0.71 (0.31 - 1.64)	0.56 (0.49 – 0.62)	0.421
More than 60 minutes	0	1.30 (0.70 - 2.41)		0.401

§ ordered as <7d, 7 – 30d, 30d – 1yr, >1yr and never (analyzed as continuous and coded and 1-5, respectively)

MUAC = mid-upper arm circumference; HR = heart rate; RR= respiratory rate; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 3. Models developed for prediction of 6 month post-discharge mortality

Variable	Regression Estimate	p-value	OR (95% CI)
Model 1 – Primary model, Intercept = 7.7172			
MUAC	-0.0462	<0.0001	0.95 (0.94 – 0.97)
SpO2	-0.0411	0.0029	0.96 (0.93 – 0.99)
Time since last hosp.	-0.2775	0.0085	0.76 (0.62 – 0.93)
HIV positive	1.0915	0.0064	2.98 (1.36 – 6.53)
Abnormal BCS	0.8723	0.0150	2.39 (1.18 – 4.83)
Model 2 – Model without SpO2, Intercept = 4.4538			
MUAC	-0.0505	<0.0001	0.95 (0.94 – 9.97)
Time since last hosp.	-0.2503	0.0153	0.78 (0.64 – 0.95)
HIV positive	1.0902	0.0061	2.98 (1.37 – 6.48)
Abnormal BCS	1.0664	0.0022	2.91 (1.47 – 5.75)
Model 4 – Model without HIV, Intercept = 8.2813			
MUAC	-0.0492	<.0001	0.95 (0.94 – 0.97)
SpO2	-0.0412	0.0027	0.96 (0.93 – 0.99)
Time since last hosp.	-0.2870	0.0058	0.75 (0.61 – 0.92)
Abnormal BCS	0.8040	0.0248	2.23 (1.11 – 4.51)
Model 4 – Model without clinical variables, Intercept = 4.4511			
MUAC	-0.0492	<.0001	0.95 (0.94 – 0.97)
HIV positive	1.0143	0.0108	2.76 (1.26 – 6.01)
Time since last hosp.	-0.2458	0.0164	0.78 (0.64 – 0.96)

MUAC = mid-upper arm circumference; BCS = Blantyre coma score

Table 4. Model Characteristics at probability cut-offs ensuring model sensitivity of greater than 80%

Model	AUC (95% CI)	Prob. cut-off	Sens. (95% CI)	Spec. (95% CI)	PPV	NPV
1	0.82 (0.75 – 0.87)	0.035	82.0 (72.3 – 91.6)	66.2 (63.5 – 68.9)	11.1	98.6
2	0.81 (0.75 – 0.87)	0.040	80.3 (70.4 – 90.3)	67.5 (64.8 – 70.2)	11.3	98.5
3	0.80 (0.74 – 0.86)	0.031	80.3 (70.4 – 90.3)	63.4 (60.7 – 66.2)	10.2	98.4
4	0.80 (0.73 – 0.86)	0.035	82.0 (72.3 – 91.6)	61.4 (58.6 – 64.2)	9.9	98.5

AUC = area under the receiver operator characteristic curve; Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value

Acknowledgments: We gratefully acknowledge the contributions of Annet Twinomuguni, Justine Kamazima, Agaba Collins, Clare Komugisha, Solome Kobugyenyi, Alexander Mutungi and Hassan Bariahikwa. Without their dedication this study could not have been completed

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: This study was internally funded. M Wiens was supported by a fellowship from the Canadian Institutes of Health Research, the Michael Smith Foundation for Health research and the Canadian Child Health Clinician Scientist Program.

Contributor Statement

Design: MO Wiens, E Kumbakumba, CP Larson, JM Ansermino, J Singer, H Wong, A Ndamira, J Kabakyenga, N Kissoon, J Kiwanuka

Data Collection: MO Wiens, E Kumbakumba, JM Ansermino

Analysis: MO Wiens, Analysis, J Singer, H Wong, G Zhou

Drafting of initial manuscript: MO Wiens

Reviewing and revising manuscript: MO Wiens, E Kumbakumba, CP Larson, JM Ansermino, J Singer, N Kissoon, H Wong, A Ndamira, J Kabakyenga, G Zhou, J Kiwanuka

Approval of final manuscript: All Authors

Data Sharing: No additional data available

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015;385(9966):430–40.

2. Wang H, Liddell C a, Coates MM, Mooney MD, Levitz CE, Schumacher AE, et al. Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;957–79.

3. Wiens M, Pawluk S, Kissoon N. Pediatric Post-Discharge Mortality in Resource Poor Countries: A Systematic Review. PLoS One [Internet]. 2013 Jan [cited 2014 Jun 19];8(6):e66698.

4. Karlen W, Dumont G, Petersen C, Gow J, Lim J, Sleiman J, et al. Human-centered phone oximeter interface design for the operating room: Pulse Oximeter Interfaced to a Mobile Device for Anesthesia Monitoring in the Developing World. Proceedings of the International Conference on Health Informatics. Rome, Italy: SciTePress; 2011. p. 433–8.

5. The WHO Child Growth Standards [Internet]. 2006 [cited 2015 Mar 1]. Available from: http://www.who.int/childgrowth/standards/en/

6. Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, MacOnochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: A systematic review of observational studies. Lancet. 2011;377(9770):1011–8.

7. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114:555–76.

8. National Implementation Guidelines for HIV Counselling and Testing in Uganda [Internet]. Kampala, Uganda; 2010. Available from: http://library.health.go.ug/publications

9. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.

10. Wiens MO, Kissoon N, Kumbakumba E, Singer J, Moschovis P, Ansermino JM, et al. Selecting candidate predictor variables for the modelling of post-discharge mortality: A protocol development project. Submitted. 2015.

11. Hosmer DW, Lemeshow S. Goodness of fit tests for the multiple logistic regression model. Commun Stat - Theory Methods. 1980;9(10):1043–69.

12. Van Buuren S, Groothuis-Oudshoorn K. Multivariate Imputation by Chained Equations. J Stat Softw. 2011;45(3):1–67.

13. Stone M. An Asymptotic Equivalence of Choice of Model by Cross-Validation and Akaike's Criterion. J R Stat Soc Ser B-Methodological. 1977;39(1):44–7.

14. Shibata R. Bootstrap estimate of Kullback-Leibler information for model selection. Stat Sin. 1997;7:375–94.

15. World Health Organization. Integrated Management of Childhood Illness: distance learning course. Geneva: World Health Organization; 2014.

16. Nguyen DTK, Leung KK, McIntyre L, Ghali W a., Sauve R. Does Integrated Management of Childhood Illness (IMCI) Training Improve the Skills of Health Workers? A Systematic Review and Meta-Analysis. PLoS One. 2013;8(6).

17. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet [Internet]. Elsevier Ltd; 2010;376(9755):1838–45.

18. Obasola OI, Mabawonku I, Lagunju I. A Review of e-Health Interventions for Maternal and Child Health in Sub-Sahara Africa. Matern Child Health J. 2015;In press. Available from: http://link.springer.com/10.1007/s10995-015-1695-0

19. Mitchell M, Hedt-Gauthier BL, Msellemu D, Nkaka M, Lesh N. Using electronic technology to improve clinical care - results from a before-after cluster trial to evaluate assessment and classification of sick children according to Integrated Management of Childhood Illness (IMCI) protocol in Tanzania. BMC Med Inform Decis Mak. BMC Medical Informatics and Decision Making; 2013;13(1):95.

20. Moïsi JC, Gatakaa H, Berkley JA, Maitland K, Mturi N, Newton CR, et al. Excess child mortality after discharge from hospital in Kilifi, Kenya: a retrospective cohort analysis. Bull World Health Organ. 2011;89(10):725–32.

21. Islam MA, Rahman MM, Mahalanabis D, Rahman a K. Death in a diarrhoeal cohort of infants and young children soon after discharge from hospital: risk factors and causes by verbal autopsy. J Trop Pediatr. 1996 Dec;42(6):342–7.

22. West TE, Goetghebuer T, Milligan P, Mulholland EK, Weber MW. Long-term morbidity and mortality following hypoxaemic lower respiratory tract infection in Gambian children. Bull World Health Organ. 1999 Jan;77(2):144–8.

23. Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. Am J Trop Med Hyg. 2012;86(5):756–63.

24. Keusch GT, Denno DM, Black RE, Duggan C, Guerrant RL, Lavery J V, et al. Environmental Enteric Dysfunction: Pathogenesis, Diagnosis, and Clinical Consequences. Clin Infect Dis. 2014;59(Suppl 4):207–12.

25. Kosek M, Guerrant RL, Kang G, Yori PP, Gratz J, Gottlieb M, et al. Assessment of Environmental Enteropathy in the MAL-ED Cohort Study: Theoretical and Analytic Framework. Clin Infect Dis. 2014;59(Suppl 4):239–47.

26. Jones KD, Thitiri J, Ngari M, Berkley JA. Childhood malnutrition: Toward an understanding of infections, inflammation, and antimicrobials. Food Nutr Bull. 2014;35(2):64–70.

27. Nair H, Simões E a F, Rudan I, Gessner BD, Azziz-Baumgartner E, Zhang JSF, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet. 2013 Apr 20;381(9875):1380–90.

Figure 1. Consort diagram of study flow
338x190mm (300 x 300 DPI)

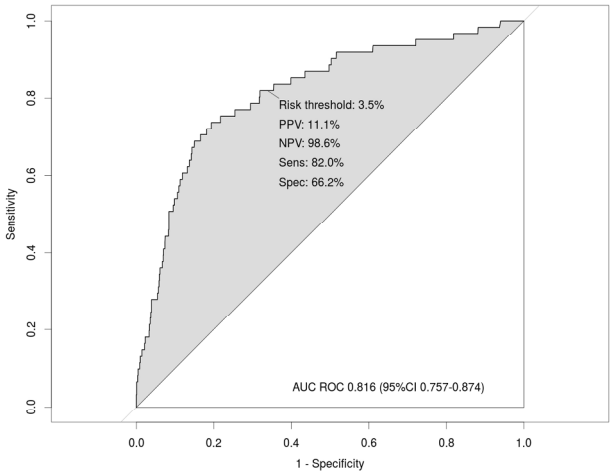


Figure 2. Performance of the primary prediction model derived with data from admission. ROC = receiver operating characteristic. Sens = sensitivity. Spec = specificity. NPV = negative predictive value. PPV = positive predictive value.
338x190mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(*c*) Explain how missing data were addressed	11
		(*d*) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			10

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	11/12
Outcome data	15*	Report numbers of outcome events or summary measures over time	11/12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11/12
		(*b*) Report category boundaries when continuous variables were categorized	11/12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			13
Key results	18	Summarise key results with reference to study objectives	13
Limitations			15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.