CHILDHOOD MORTALITY FROM ACUTE INFECTIOUS DISEASES IN UGANDA: STUDIES IN SEPSIS AND POST-DISCHARGE MORTALITY

by

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Abstract

Background and objectives

The fourth Millennium Development Goal to reduce childhood mortality by two-thirds will not be achieved in most countries of sub-Saharan Africa. Infectious diseases are the most common cause of death in these children. A significant period of vulnerability occurs in the weeks and months following discharge. We sought to characterise mortality both in-hospital and post-discharge in children admitted with infectious diseases and develop prediction models for these outcomes.

Methods

The primary study was a cohort study of children 6 months to 5 years of age admitted with proven or suspected infections. Children were followed throughout hospitalization and until six months post-discharge. Prediction models for in-hospital and post-discharge mortality were developed using standard logistic regression techniques. A further prospective cohort study was conducted to determine morbidity, mortality and health seeking following pediatric outpatient department visits in a rural health facility.

Results

The primary cohort study enrolled 1307 subjects who were admitted with a proven or suspected infection. Sixty five (5.0%) children died in hospital and 61 (4.9%) of children died during the six month post-discharge period. Parsimonious models were developed for both in-hospital and post-discharge mortality. Variables for in-hospital prediction included Blantyre coma score, weight for age z-score, and HIV status. Variables for post-discharge prediction included Blantyre coma score, mid-upper arm circumference, HIV status, oxygen saturation and time since last hospitalization. Both models performed well with areas under of receiver operating characteristics curve of 0.85 and 0.80, respectively. Most (65%) post-discharge deaths occurred outside of a hospital. The secondary study of out-patient department visits included 717 sick-child visits and found that mortality and subsequent admission over 30 days occurs after approximately 2% of visits. Health seeking occurred in 7% of sick-child visits. No baseline clinical factors were associated with outcomes following these visits.

Interpretation

The derived models can be used to develop effective interventions to improve in-hospital care, referral of admitted subjects to higher levels of care, and post-discharge care. Further research is required to better understand health seeking following out-patient department visits.

Preface

Chapter 1

Portions of chapter 1 were included in a portion of a published work by Matthew Wiens. Wiens MO, Kumbakumba E, Kissoon N, Ansermino JM, Ndamira A, Larson CP. Pediatric sepsis in the developing world: challenges in defining sepsis and issues in post-discharge mortality. Clinical Epidemiology. 2012:4(1) Pages 319 - 325. This was a narrative review article which was written by Matthew Wiens and reviewed and edited by all co-authors.

Chapter 2

A version of Chapter 2 has been published. Wiens MO, Pawluk S, Kissoon N, Kumbakumba E, Ansermino JM, Singer J, Ndamira A, Larson CP. Pediatric Post-Discharge Mortality in Resource Poor Countries: A Systematic Review. PLoS ONE. 2013;8(6):e66698. This study was conceived, designed, analysed and written by Matthew Wiens. Co-authors reviewed and edited the manuscript. Shane Pawluck assisted with the implementation of the search strategy, the review of retrieved articles and the abstraction of the data from eligible articles.

Chapter 3

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Chapter 4

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Chapter 7

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Chapter 10

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S. D. G.

Dedication

To the children of Uganda

Chapter 1. Problem overview and research goals

The Millennium Development Goals (MDG), established following the United Nations Millennium Summit in 2000, contain eight international development goals. These include (1) reducing poverty and hunger, (2) increasing access to education, (3) promoting gender equality, (4) improving child health, (5) improving maternal health, (6) improving the treatment of malaria and HIV, (7) improving environmental sustainability and (8) building global partnerships for development. All 193 United Nations member states committed to help achieve these goals. The fourth of these goals, improving child health, specifically commits to achieving a two-thirds reduction in under-five mortality by 2015, compared to 1990 levels.[1] Using member country submitted reports and other data, the United Nations produces an annual MDG report summarizing the overall progress towards achieving each MDG.[2] Detailed region, sub-region and country analyses of progress and projections are also produced by other groups including the Global Burden of Diseases Project and the Institute for International Programs.

The Global Burden of Diseases (GBD) project provides comprehensive global and regional estimates of mortality, diseases, injuries and risk factors. Following national and international efforts, the Global Burden of Diseases project estimates that global under-5 mortality has reduced from approximately 85 deaths per 1000 live births in 1990 to approximately 44 deaths per 1000 live births in 2013, an annualized rate of decrease of 2.8%.[3] While this decrease is not insignificant, it is far below the two-thirds reduction goal set during the millennium summit. Further, this distribution has not been uniform across the various regions. Among the 138 least developed countries, only 27 are likely to achieve the target of a two-thirds reduction in under-5 mortality. Of these 27 countries only two (Liberia and Benin) are in the Sub-Saharan African region (out of 48 countries). The disproportionate distribution of child-mortality gains has resulted in an increasing proportion of children who die in Sub-Saharan Africa relative to other regions. In 1990, approximately 30% of childhood deaths occurred in Sub Saharan Africa. This has increased to approximately 50% in 2012. The growing concentration of child mortality in this region is likely to be further exacerbated since Sub Saharan Africa is the only region in the world where the population of children is expected to rise substantially. By 2050 it is estimated Sub Saharan Africa will contain nearly 40% of all live-births and nearly 40% of all children worldwide.[4]

Causes of under-5 mortality

In 2010, nearly 75% of all childhood deaths in Africa were secondary to infectious diseases. Malaria, diarrheal diseases and pneumonia were the most important causes of infectious disease associated deaths. In 2010 malaria was estimated to be responsible for 15% of under-5 deaths.[5] A systematic analysis of malaria mortality data showed rising deaths secondary to malaria from 1980 (377,000 deaths) to 2004 (1,047,000 deaths) but subsequent reductions thereafter until 2010 (700,000 deaths). Rapid scaling of malaria control programmes that include artemisinin combination treatment, vector control and insecticide treated bed nets over the past decade in Africa has led to significant declines in malaria associated deaths throughout Africa in recent years.[6]

Pneumonia is estimated to be the cause of death in 17% of children who die in Africa each year, the single most important cause of childhood death in Africa.[5] While significant reduction in pneumonia associated deaths in Africa has occurred, this reduction as not occurred as rapidly as for malaria associated deaths. The annualized rate of decline is estimated to be 1.8% between 2000 and 2010, compared to an annualized decline of 2.7% for malaria. A significant barrier in addressing pneumonia mortality is that many deaths occur outside of a hospital context, possibly during the post-discharge period. Although over 60% of children with severe pneumonia are treated in hospital, over 80% of the deaths associated with severe pneumonia occur in the community.[7] Poor availability of oxygen at community based health facilities and a high prevalence of malnutrition are a further barriers in achieving better outcomes as both hypoxia and malnutrition are each associated with a 15 fold increase in odds of mortality during the acute phase of the disease compared to children without these additional risk factors.[8]

Diarrheal diseases account for approximately 11% of under-5 deaths in Africa and have been reducing at an annualized rate of 3.7% per year since 2000. It is thought that much of this reduction has been due to socioeconomic and environmental improvements over the past decade.[9] The most common cause of severe and fatal diarrhea is rotavirus, associated with close to 30% of all deaths, and has been a primary incentive in introducing and scaling the rotavirus vaccine. Addressing issues related to nutrition is an important barrier in achieving further reductions in diarrhea associated death.

HIV/AIDS is responsible for approximately 4% of under-5 deaths in Africa and has been declining rapidly in recent years. It is estimated that this decline between 2000 and 2010 is 6.4% per year, a rate high enough to achieve the 2015 MDG target.[5] Much of the success of this reduction can be credited to aggressive scaling up of prevention of mother to child transmission in several African countries.

Childhood nutrition

Moderate or worse stunting (height for age z-score < -2), being underweight (Weight for age z-score < -2) and wasting (Weight for height z-score < -2) are highly prevalent, estimated to affect 35%, 18% and 9% of African children in 2011, respectively.[10] It is well recognized that malnutrition is a significant contributor to 45% of all childhood deaths, and most childhood deaths from infectious diseases.[10] A recent analysis of 10 prospective studies in Africa, Asia and South America evaluated the impact of stunting, underweight and wasting on mortality in children 1 week to 5 years of age and found that increasing degrees of anthropometric abnormality (stunting and wasting) are associated with increasing hazard of death from all causes, particularly pneumonia and diarrhea.[11]

The interplay between nutritional status and childhood mortality from infectious diseases is complex and poorly understood. It is generally accepted that a vicious cycle exists between malnutrition and infection. Acute infectious episodes exacerbate malnutrition through various mechanism including anorexia, poor nutrient absorption and increase nutrient loss through diarrhea. While the contribution of malnutrition to an increased susceptibility to infections is well recognized, it's mechanism is still an active area of investigation.[12] A renewed interest in environmental enteropathy (also called tropical enteropathy or environmental enteric dysfunction) has provided, and continues to provide, some insights into the mechanisms of this cycle. Environmental enteropathy is a syndrome similar to a mild form of celiac disease and was first described in the 1950s among people living in poor, generally tropical, countries. Almost all individuals in these countries had a generalized loss of intestinal integrity characterized by reduced absorptive capacity, increased permeability and inflammation.[13] Children living in conditions of poor hygiene often develop environmental enteropathy soon after birth leading to impaired growth, initiating the vicious cycle of malnutrition and infection. Chronic systemic inflammation develops following microbial translocation secondary to reduced intestinal

integrity leading to increased vulnerability to infection and furthering under nutrition. In addition to environmental enteropathy as a causal factor in malnutrition, it is also associated with a poor response to nutritional intervention.[14] This assertion is supported by a mathematical modeling of existing literature of nutritional interventions including micronutrient supplementation (to child and pregnant mother), balanced energy protein supplementation, complimentary feeding and breastfeeding promotion that found that the scaling of these interventions to 99% coverage worldwide would only reduce stunting by 33% at 12 months.[15] Environmental enteropathy is also thought to be associated with poor response to other interventions such as a decrease in the efficacy of the oral rotavirus vaccine compared to populations in western countries.[16]

Post-discharge vulnerability

In resource poor countries very little focus has been placed on what happens to children in the weeks to months post-discharge following hospitalization for a serious infectious illness. However, while not the primary objective, several studies in Africa and Asia, studying a variety of pediatric populations, have found significant vulnerability to both re-hospitalization and mortality in the weeks and months following discharge. These studies suggest that the probability of mortality may be as high in the post-discharge period as during the hospitalization period. However, these studies are limited by various factors such as low rates of post-discharge follow-up, inclusion of subjects without infectious diseases (ex. injury, poisonings, isolated malnutrition) and interventional study designs such as randomized controlled trials (reducing external validity). No studies focusing on post-discharge vulnerability in a general post-acute infectious disease population currently exist.

A 1996 cohort study examined childhood mortality during and after hospitalization in western Kenya, with the intent to determine the therapeutic effect of malaria treatment regimens.[17] Although this study was not designed to elucidate the general burden of disease following discharge from hospital, both baseline demographic and diagnostic information as well as post-discharge vital status allow important conclusions to be drawn in this regard. Among the 1223 children admitted to hospital during the observation period 23% died between admission and eight weeks post-discharge, with 10% of the of deaths occurring in hospital and 13% of the deaths within eight weeks following discharge. The largest risk factor for mortality in this study was baseline bacteremia. Patients with bacteremia had a case fatality rate of 35% and accounted

for 23% of inpatient deaths and 17% of outpatient deaths. The outcomes of this study reflect results of a more recent study from 2005 examining the effect of community acquired bacteremia among nearly 20,000 children admitted to a district hospital in Kilifi, Kenya.[18] Although this study did not conduct post-discharge follow up, the overall in-hospital mortality rate of 7.1% and the mortality rate of 28.2% among bacteremic patients, suggest that the burden of post-discharge morbidity and mortality will likely remain substantial. Recently, the Kilifi Health and Demographic Surveillance Study which collects information on births, deaths and migrations in a population of 240,000 people was linked to the Kilifi district hospital database and a retrospective cohort analysis of post-discharge deaths was conducted.[19] This study reported a post-discharge mortality rate of 4.5% among all children less than 15 years of age. The most important risk factors for mortality after discharge included malnutrition (as measured by weight for age z-score), hypoxia and bacteremia.

Proper post-discharge follow-up is scarce and is further influenced by poor access to quality health services. A study conducted in Guinea Bissau carried out between 1991 and 1996 using a population registry found that among 3647 children discharged, there were 221 (6.1%) deaths during the post-discharge period of 12 months, one third of which occurred within two weeks of discharge.[20] Most of these deaths (77%) occurred in their homes/communities rather than during a re-admission (14.5%). This study also identified some risk factors for post-discharge mortality and found that lower age, ethnicity, lower maternal education, discharge without authorization and a diagnosis of anemia or diarrhea were associated with increased post-discharge mortality.

Disease specific studies have been conducted with mixed results relating to post-discharge mortality. A re-analysis of a randomized controlled trial of vitamin A intervention in children under five living in Tanzania presenting with pneumonia showed that among all patients, intervention and control, the hospital mortality was approximately three percent with a 24 month post-discharge mortality rate of over 10 percent (most occurring within the first several months).[21] Despite the significant effect of HIV on overall mortality in this study, several other factors were independently associated with death including pneumonia severity as defined by respiratory rate, hyperthermia and hypoxemia. Another study from Guinea Bissau examined the effect of a financial incentive on childhood mortality from malaria.[22] This study showed that among all patients (control and intervention), the in-patient mortality was approximately 7.5%

during the in-patient phase and approximately 2% at day 28. With a mean length of stay of 8 days this indicates an approximation of three week post-discharge mortality.

A recent study in Malawi conducted between 2002 and 2006 examined the association between in-patient and post-discharge mortality among children with severe anemia.[23] Three hundred and fifty three children aged 6 months to 5 years of age were followed for 18 months post-discharge. In this study the in-patient mortality rate was 6% and the post-discharge mortality rate was 12%. With nearly 18% loss to follow up, this is likely an underestimate. While it is difficult to make a justified correlation between outcomes among those with anemia compared with infectious diseases, the high proportion of bacteremia, malaria and HIV in this cohort (15%, 59% and 13% respectively) is quite convincing that infections would have contributed to some deaths.

An improved understanding of post-discharge vulnerability among children in resource poor countries could play a significant role in designing interventions to reduce this risk. Specifically, the identification of risk factors for morbidity and mortality could be used to create prediction tools to aid in identifying vulnerable children. The stratification of children based on their level of vulnerability could be used to create interventions that maximize efficient use of scarce resources, a critical component of any scalable health intervention.

Sepsis syndrome

Sepsis, as defined by the international pediatric sepsis consensus conference, is the systemic inflammatory response syndrome (SIRS) in the presence of a suspected or proven infection.[24] Sepsis can be due to any infectious etiology, but in developed settings it is most often bacterial whereas in the developing world co-infection is common and viral or parasitic infections also play a significant role. Most under-five childhood deaths in developing countries can be attributed to deterioration along the sepsis pathway (infection to sepsis to severe sepsis and septic shock with progressive organ failure). However, pediatric sepsis is rarely discussed as a leading cause of death in developing countries, with the notable exception of neonatal sepsis. Instead, clinical and research programs are vertical in nature, attempting to address specific infectious diseases such as malaria, pneumonia or diarrhea and thus often neglect the common syndromic similarities of severe infectious disease – an inflammatory response that, if left uninterrupted, often leads to progressive organ dysfunction, shock and death. The limitations of this vertical

focus are further compounded by the fact that many available diagnostic tests are often not able to differentiate between vertical diseases.[25,26] Furthermore, children with sepsis are often co-infected with multiple pathogens, such as malaria and bacteremia, limiting the effect of vertical treatments.

The current pediatric sepsis definitions (i.e., sepsis, severe sepsis and septic shock) have evolved primarily as an identification tool for inclusion of children in clinical trials of sepsis interventions, such as activated protein C, rather than for clinical use.[24] They were originally defined based on the adult definition for sepsis developed in 1992.[27,28] Despite the fact that these definitions were designed for research purposes, they are often used clinically in developed nations for the identification of children who require urgent intervention to stop the progressive inflammatory response. More importantly, they form the basis for guideline development aimed at treating the various stages of the sepsis continuum. In both the adult and pediatric definitions of sepsis, meeting two of four criteria is required to diagnose SIRS, and therefore sepsis (**Table 1.1**). These criteria are based on temperature, heart rate, respiratory rate, and leukocyte count. One major difference between the adult and pediatric SIRS definition, apart from age-specific cut-offs, is that the pediatric definition required either an abnormal leukocyte count or abnormal temperature for a diagnosis of SIRS (in adults, meeting any two criteria of four was sufficient). This was important since it was recognized that derangements in heart rate and respiratory rate are common and do not necessarily denote a significant inflammatory process. It is recognized that defining sepsis, and its various stages is an iterative process in continual need of refinement.[28] More importantly it must also be recognized that sepsis definitions should be specific to a region's resource capacity, much the same way that sepsis treatment guidelines are specific to low versus high resource settings.[29–32]

Of the three sepsis categories defined in the international pediatric sepsis consensus conference (sepsis, severe sepsis, and septic shock) all require laboratory tests (e.g., leukocyte count). In addition, severe sepsis and septic shock require complex organ dysfunction criteria that could only be determined at highly resourced institutions. In many developing countries, even simple laboratory tests, such as leukocyte counts, are often not measured since public sector systems and patients cannot afford them. A further limitation in using the traditional sepsis definition is the requirement for a core temperature measurement. While probably ideal, the additional time and

care required to obtain this, coupled with potential complications of rectal measurements make a strong case for validation of axillary or oral temperature measurements. With this in mind, sepsis research aiming to influence clinical practice must include considerations of the definitions being used and their applicability to the population being studied. Since sepsis forms the final common pathway of infectious disease mortality, a more pragmatic alternative for the identification of children at high risk of infectious disease related mortality may be justified.

Research goals

Systematic review of existing literature on post-discharge mortality

To better understand both the burden of post-discharge mortality and to gain insights into potential solutions, a systematic review on studies examining post-discharge mortality in resource poor countries is required. Few studies of post-discharge mortality exist and those that do, study heterogeneous populations using a variety of study designs. Studies of post-discharge mortality are often disease specific, making comparisons between studies difficult. It is necessary, thus, to determine the overlapping and non-overlapping risk factors for post-discharge mortality among the important disease subgroups including pneumonia, diarrhea and malaria.

Heterogeneity in study design generally stems from differences in the primary objectives of existing post-discharge mortality research. This design heterogeneity can also influence the results of these studies. Randomized controlled trials of interventions occur in highly controlled environments and even when the intervention is not aimed at improving morbidity or mortality following discharge, these studies preclude direct comparisons with studies using surveillance data where the environment is closer to what would be expected to occur naturally. The assessment of associated risk factors collected with varying degrees of rigor among similar populations also presents difficulties if the study designs differ substantially (RCT vs retrospective cohort study). A further difficulty in understanding the current state of the evidence is that many studies examine post-discharge mortality as secondary outcomes and may therefore not be readily accessible without a thorough literature search. Finally, since mortality following discharge is generally under-recognized by both researchers and policymakers a systematic compilation of existing literature can serve to create better awareness of this important outcome.

Evaluation of pediatric post-discharge mortality

There is a paucity of high quality research on post-discharge mortality. Existing studies are often disease specific (i.e. malaria or pneumonia), and use various, and often complex, criteria to determine eligibility. 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. With an ultimate objective of the identification and treatment of vulnerable children, it is of critical importance to have a body of high-quality research on populations of children in whom interventions can be both studied and implemented. Some studies, while including a more general population, include children both with and without infectious diseases. Combining admissions secondary to conditions such as trauma, congenital diseases, and cancer is likely to result in biased assessments of risk factors for post-discharge mortality that would be applied to children following acute infectious illness. To date there are no studies examining post-discharge mortality in a cohort of children admitted with a serious infectious disease.

In addition to defining a population of interest in whom to study post-discharge mortality, the design must also be appropriate. Since many existing studies were not designed to answer questions of post-discharge mortality, their results are less likely to be free of bias. Randomized controlled trials of interventions produce artificially controlled environments whereby even those in a control group receive care not typical for their environment.[33] In retrospective studies, while the environment may be reflective of standard care, variables are not rigorously assessed and outcomes are often not determined on all subjects. In resource poor countries without national vital statistics databases ,mortality after discharge can become very difficult to determine, with many studies unable to determine this outcome in as many as 40% of study subjects.[34] A well designed prospective cohort study using high quality methods of data collection and an exhaustive determination of mortality statistics on discharged children is, therefore, critically important as researchers and policy makers seek to improve morbidity and mortality in children following discharge.

Derivation of risk stratification models for post-discharge mortality

A critical first step in the both the development and implementation of post-discharge interventions is to determine the population in whom such interventions should be applied. While

it is readily apparent that all children who are discharged have a substantial risk of death in the weeks and months after discharge, it is not practical to create complex interventions to be applied to all discharged children. Interventions including counselling mothers on illness recognition and timely health seeking is important and should be incorporated into routine discharge counselling. However, interventions such as delayed discharge, pharmacologic prophylactic therapy, or post-discharge follow-up require substantial resources and could be more efficiently incorporated into care using predictive tools. In countries where resources are scarce, interventions must be developed to create maximal impact using few resources.

Prediction modelling is often used to determine populations at greatest risk, in whom interventions should be applied. This process requires rigorous data collection and outcome assessment. It also requires a thorough understanding of potential predictors of the outcome to maximise the probability that a suitable model can be developed. Further, in a resource poor context, the predictors must be easily and reliably measured. Finally, the prediction model must be easily applied.

Determination of morbidity, mortality and health seeking following outpatient department visits

Most children who receive medical care in resource poor countries do so at rural lower-level health facilities. Most rural, lower-level health facilities in countries such as those in Uganda operate primarily as outpatient departments.[35] Few rural in-patient beds means that children with significant risk of morbidity or mortality may be referred to higher-level health facilities, which can incur significant costs for families. While it is important to characterize the epidemiology of morbidity and mortality following hospital discharges, significant morbidity and mortality may also occur following outpatient department (OPD) visits. To date, no studies have examined the prevalence of hospitalization and mortality after community level outpatient care. Studies exploring risk factors for post OPD morbidity and mortality are therefore required. An exploratory study including children seen at an outpatient clinic and following them for a period of time following the sick-child visit would be an important first step in this process.

Evaluation of sepsis criteria in hospitalized children as it relates to in-hospital mortality

The current sepsis definitions were originally developed for use in adults in order to create suitable populations for conducting infectious diseases-based research. These definitions have

been largely adopted into the pediatric context and while they do provide entry criteria for clinical research they are also used in the development of treatment guidelines, and indirectly, as prognostic indicators. The first stage along the sepsis continuum (sepsis, severe sepsis, septic shock) is the presence of the systemic inflammatory response syndrome (SIRS) along with a proven or suspected infection. Most deaths due to infectious diseases are attributable to sepsis, but sepsis remains a poorly recognized syndrome worldwide.[36–38] The World Health Organization has not recognized sepsis as a separate topic on the World Health Organization website.[39] An understanding of sepsis as being the cause of most infectious diseases associated deaths is by definition, an understanding that the underlying process of progressive inflammation and organ dysfunction is common to most infections as they progress from mild to severe. It would be generally assumed, therefore, that admitted patients failing to meet the first stage of sepsis (SIRS), would be at a much lower risk of infectious diseases related mortality than someone meeting these criteria. This assumption has never been tested in a resource poor context where the unique interplay between factors such as malnutrition and infectious diseases and major differences in the etiology of infectious diseases exist. If these definitions fail to add significant prognostic benefit, their adoption would not be warranted and alternative methods of classifying infectious disease mortality risk must be sought. However, if these definitions work well in a resource poor context, the scaling of such classifications could improve standardization of infectious disease mortality risk.

Derivation of risk stratification models for pediatric in-hospital mortality

Infectious disease risk classification is extremely important in the resource poor context. For the provision of efficient and effective health care, those individuals with high risk of morbidity and mortality must receive priority for scarce resources. It is widely accepted that some resources, such as oxygen, are poorly distributed. The accurate detection of hypoxemia in the absence of pulse oximetry (common in resource poor settings) is poor and many children who require oxygen do not receive it, and likewise, many children who do receive oxygen do not require it.[40] While risk scoring tools for in-hospital mortality prediction exist in resource rich countries, these are not valid in the resource poor context and new, context specific, tools are required to allow for improved utilization of hospital resources.

It is clear from existing research on post-discharge mortality that there will be important overlap in risk factors predicting in-hospital mortality and post-discharge mortality. Risk factors such as oxygen saturation are known to reflect disease severity and risk of death during the acute phase of disease. Post-discharge mortality literature also suggests that oxygen saturation is an important predictor of post-discharge mortality.[19] The integration of prediction models for both in-hospital and post-discharge mortality could provide added benefit of risk prediction in two contexts with little additional model input requirements.

A further benefit of risk modeling mortality among admitted children is its utilization for the generation of referral recommendations for children admitted to health centers in rural settings. Currently, referral recommendations are often based on the integrated management of childhood illness (IMCI) guidelines.[41] These guidelines form the basis of treatment standardization in many resource poor countries. Referral criteria, however, are complex and disease specific, and include signs and symptoms with varying degrees of severity and interpretability. The use of a simple risk-scoring tool of 4 or 5 easily measured variables, which can be applied to any admitted subject with an infectious illness, may increase the probability that children with high risks of morbidity and mortality are referred in a timely fashion. While such research should, ideally, be conducted within rural health centers, this is not feasible during initial phases of research and initial explorations are best done in hospitals with sufficient volume and severity of patients.

Chapter 2. Pediatric post-discharge mortality in resource poor countries: A systematic review

Background

Acute diseases leading to death and significant morbidity continue to plague children in resource limited areas of the developing world disproportionately. Worldwide, and in particular in Africa, infectious diseases are the most common cause of childhood mortality.[3] While effort has been made to address diagnosis and treatment during the acute episode, care following discharge from hospital is an important aspect of management that is often neglected by both policy makers and health researchers. Reasons for this neglect are likely multifactorial and include a tremendous burden and high costs to provide care for acute illness, which in regions with limited resources poses significant system challenges. Furthermore, failure to recognize and document the burden of post-discharge morbidity and mortality contributes to a lack of awareness by health care workers of potentially avoidable adverse outcomes. Therefore, the attempt to improve care following discharge may be viewed as a low priority by both health care workers and policy makers. Lack of attention to post-discharge issues has tremendous adverse implications because the available evidence strongly suggests that in developing countries post-discharge deaths may be of similar (or higher) magnitude than deaths during hospitalization.[17,21,23,42,43] These data suggest that improved discharge planning and post-discharge care has the potential to decrease the need for readmission, and to significantly decrease morbidity and mortality. This discharge process will be an important step in achieving the fourth millennium development goal (MDG) of a two thirds reduction in under-five mortality.[1]

While current evidence clearly points to the significant burden of post-discharge mortality, the estimates of this burden vary widely between studies. Population factors such as age distribution, co-morbidities, disease severity, healthcare resources, and social disparities play a significant role in the rate of post-discharge mortality. Further, differences in the design of studies can contribute to variation in the estimates. Studies are interventional in nature (such as randomized controlled trials) are unlikely to reflect the true baseline risk, even in a control group. While retrospective studies are free from such biases, the methods of data collection are less robust and can also lead to biased estimates. Finally, both time period and location often reflect significant

differences in the standards of care and therefore the rates of the outcomes of interest. For these reasons, a concise summary of the state of the evidence is required to better able to inform future policy and research.

The Meta-analysis of Observational Studies in Epidemiology Group have created guidelines for the reporting of meta-anlaysis of observational studies.[44] The proposed reporting checklist includes 6 primary sections including (1) reporting of background, (2) reporting of search strategy, (3) reporting of methods, (4) reporting of results, (5) reporting of discussion and (6) reporting of conclusions. Following these guidelines, we systematically reviewed the literature for studies reporting pediatric post-discharge mortality in resource poor countries. Our primary objective was to describe the rates of mortality following medical discharge in children and identify the risk factors which are associated with post-discharge mortality.

Methods

Search strategy

We conducted a systematic computerized search from the inception date (1946 in MEDLINE and 1974 in EMBASE) to October, 2012 to identify all potentially eligible studies. One investigator trained in database searching independently carried out an initial systematic search. A study was defined as an analysis of post-hospitalization mortality in a pediatric population. We applied the following algorithm in both medical subject heading (MeSH) and free text words. In MEDLINE, the MeSH terms "follow-up studies", "hospitalization", OR "longitudinal studies" were combined with "developing countries", "Africa", "Bangladesh" , "Haiti", "Afghanistan", "Yemen", "Papua New Guinea", "Myanmar", "Pakistan", OR "Solomon Islands". MeSH terms were exploded where appropriate. The MeSH term "Africa" included the names of all African countries when exploded. Free text words including "post-discharge mortality" and "long-term outcomes" were also used to increase capture of relevant articles. In EMBASE, the MeSH terms "follow-up", "hospitalization", OR "longitudinal study" were combined with "developing country", "Bangladesh", "Haiti", "Afghanistan", "Yemen", "Papua New Guinea", "Burma", "Pakistan", "Solomon Islands" OR "Melanesia" AND "Pediatrics". Free text word "Burma" was also included in the search as this was not a MeSH term. Google Scholar™ was also searched and references of relevant publications were reviewed to identify

any articles not captured during initial search. All retrieved articles were independently reviewed by a second author to determine if they met inclusion criteria.

Inclusion criteria

Studies were included if: (i) they presented original data from randomized-controlled trials, cohort studies, or retrospective analyses; (ii) the data on post-discharge mortality in pediatric patients of any age was clearly defined and length of follow-up was reported; (iii) data was collected from pediatric patients living in developing countries. Developing countries were defined for the purposes of this review as those countries currently classified by the United Nations Development Program (UNDP) as having a low Human Development Index (HDI).[45]

Exclusion criteria

Studies were excluded if: (i) there was no pediatric data or pediatric data could not be differentiated for adult data; (ii) there was no post-hospital discharge information or patients were not discharged from a hospital setting; (iii) discharge was following a non-admission (i.e. following birth); (iv) studies represented a surgical population since post-discharge care following surgery would likely be very different from care following acute illness and; (v) if the study was unpublished, published in a language other than English or if published only in abstract form.

Data collection and quality assessment

Data was collected systematically onto a computerized spreadsheet developed *a priori*, which included study name and year of publication, primary author, country, number of participants, age of study population, reason for hospital admission (either medical or surgical), in-patient mortality, post-discharge mortality, post-discharge hospitalization, post-discharge observation period and risk factors of mortality. When the study was reported as the result of a randomized controlled trial, data from both the control arm and intervention arm was collected and reported either individually or as a combined estimate when appropriate.

While a validated quality scoring system for studies on post-discharge mortality has not been developed, several variables likely to contribute to study quality were collected and reported

including: proportion of subjects successfully followed-up, method of follow-up, study design and presence of an intervention.

Analysis

Since significant heterogeneity between studies was observed studies were not pooled. Studies were organized based on underlying etiology in the study sample. Descriptive statistics were generated using Microsoft Excel (Redmond, WA).

Results

Thirteen studies met both inclusion and exclusion criteria and were included in the final analysis; four randomized controlled trials,[21,22,33,42] four prospective cohort studies,[17,46,47] three retrospective cohort studies,[19,20,48] and two case-control studies with longitudinal follow-up of cases and/or controls[23,34] (**Figure 2.1**). No studies were excluded based on language of publication. Four studies were from Bangladesh, three from Guinea-Bissau, two from both Kenya and Malawi, one from Tanzania, one from the Democratic Republic of Congo and one from The Gambia. The pediatric populations which the studies represented varied widely by study according to both age and underlying disease state. The disease states represented included four studies of all children admitted to hospital; two studies of children admitted with malaria; three studies of children admitted with diarrhea; three studies of children admitted with pneumonia; one study of children admitted with anemia; and one of children admitted with malnutrition (**Table 2.1**)**.** Rates of post-discharge mortality varied widely between studies (1% - 18%) as did the durations of post-discharge follow-up (approximately 28 days – 5 years). Seven studies reported the approximate proportion of children surviving at various time-points during follow-up and reported that most children who died did so during the early phase of follow-up (**Table 2.2**). Risk factors for post-discharge mortality varied significantly between studies but the most important included young age, malnutrition, multiple previous discharges, HIV infection and pneumonia (**Table 2.3**).

Studies of all hospital admissions

Three studies (two from Kenya and one from Guinea-Bissau) included all children regardless of admission diagnosis. The first Kenyan study, a prospective cohort study conducted in 1991,

enrolled 1223 children between 0 and 5 years of age at the time of admission and followed these children until 8 weeks following discharge.[17] During this period 10% of children died during their hospitalization and 13% of children who were discharged died. The second retrospective study was conducted in 2011 in Kenya and examined 12 month post-discharge mortality between the years 2003 and 2008 among children 0 to 15 years of age.[19] Using a pre-existing surveillance system they found that mortality was 4.5%. The main strength of this study was the large number of study subjects (14,971) and the detailed analysis of post-discharge mortality risk factors. The most notable risk factors for post-discharge mortality was previous hospitalization with three or more discharges producing a hazard ratio of 23.5 (95%CI 10.70-51.84) and 2 previous discharges producing a statistically significant hazard ratio of 7.06. Very severe pneumonia and very low weight for age scores also produced statistically significant hazard ratios of 4.09 and 6.53, respectively (**Table 2.2**). The study from Guinea-Bissau was also a retrospective cohort study based on surveillance data.[20] It followed children who were primarily below 5 years of age and found that in-hospital mortality was approximately 12% while post-discharge mortality was approximately 6%. The primary risk factors for post-discharge mortality were discharge against medical advice (RR 8.51, 95% CI 5.32-13.59), anemia and diarrhea (RR 2.0 and 1.8, respectively).

Malaria studies

Two studies of children with malaria, both of which were randomized trials, were identified. The first study, conducted in Malawi between 2006 and 2009, randomized children with severe malaria to receive intermittent preventative therapy (IPTpd) or placebo following hospital discharge.[33] Over the course of six months of follow-up, similar numbers of children in both the IPTdp and placebo groups died (2.6% vs. 2.4%, respectively). Nearly 20% of children discharged required subsequent hospitalization. The second study, conducted in Guinea-Bissau between 2004 and 2006, examined the effect of a financial incentive to health care workers to improve hospital treatment of acute malaria.[22] Within 4 weeks of admission overall mortality among both groups was approximately 8.7% with a 7.2% in-hospital mortality and 2% post-discharge mortality rate. Since the period of follow-up was calculated from admission, no specific length of follow-up was conducted. Overall it was approximately 3 weeks as the mean length of stay was approximately 1 week.

Diarrhea studies

Three studies investigating outcomes following diarrhea were identified, all of which were conducted in Bangladesh between the late 1970s and the early 1990s. The most recent study conducted between 1991 and 1992 enrolled 500 urban children who were admitted and treated for diarrhea.[46] With 80% follow-up at 12 weeks post-discharge they found that post-discharge mortality was 7% and that approximately half of these deaths occurred during a re-admission (non-fatal re-admissions were not reported). This study conducted verbal autopsies and found that the primary cause of death was a diarrheal disease in 69% of cases and an acute respiratory disease in 31% of cases. Given the relatively low proportion of follow-up it is likely that the actual post-discharge mortality rate was higher. This study reported that young age, short stature for age, lack of breastfeeding, low maternal education, and female sex were all predictors of post-discharge mortality. The remaining two studies were from 1979 and 1983 and of relatively poor methodological quality.[48,49] The post-discharge mortality rates were approximately 4% and 3%, respectively, and the hospital course was not described.

Pneumonia studies

Three studies of outcomes following pneumonia were identified, two of which were randomized trials. The first study was a secondary analysis of a trial of vitamin A supplementation in children 6-60 months of age with pneumonia.[21] This study found that in-hospital mortality was 3% and post-discharge mortality was 10% after 24 months. Risk factors for post-discharge mortality were not calculated, but HIV infection (3.92 95%CI 2.34-6.55), young age (3.70, 95%CI 1.72-7.95), unclean water source (2.92, 95%CI 1.03-8.30), severe anemia (2.55 95%CI1.13-5.77), severe pneumonia (2.47, 95%CI 1.59-3.85), and nutritional indicators such as stunting (2.12, 95%CI 1.31-3.42) were associated with increased overall mortality (in-patient and post-discharge). The second study was a randomized controlled trial of in-patient versus out-patient management of severe pneumonia in Bangladesh.[42] There were no deaths during hospitalization and only 1% mortality in 180 children who were followed for 3 months following discharge suggesting that this was a low-risk group of patients. The final study was a follow-up study of a case-control study assessing predictors of hypoxemia in Gambian children.[34] The initial study, conducted between 1992 and 1994, enrolled 190 children admitted with a lower

respiratory infection. Follow-up was conducted between 1996 and 1997 during which 15% of hypoxemic children (SpO2 <90%) and 6% of non-hypoxemic children died. Differences in mean length of follow-up were observed (41 months in hypoxemic group vs. 34 months in non-hypoxemic group) and a poisson regression showed that mortality rates were not statistically significantly different. However, this was not an appropriate analysis since this assumes a constant hazard over time, an assumption unlikely to be correct for post-discharge mortality. Similar to other studies, low weight for age Z-scores during admission were associated with higher post-discharge mortality rates (RR 3.2 95% CI 1.03-10.29).

Anemia studies

One study aiming to determine the short and long term effects of severe anemia in children conducted in Malawi in 2008 was identified.[23] This study was the longitudinal part of an earlier case-control study and had two arms (cases and controls) which where independently followed for 18 months after discharge. In the anemia arm (cases) 377 children were enrolled of whom 6.4% died in hospital and 11.6% died following discharge over the course of 18 months. In the non-anemia arm (controls), consisting of children with any condition other than anemia, none of the 373 children died in hospital and 2.7% died following discharge. This study had a low rate of follow-up (approximately 80%) relative to the other studies. In the anemic group, HIV, bacteremia, and nutritional deficiency (stunting/wasting) were more common in those who died following discharge compared to survivors, however no formal analysis was done in this regard.

Malnutrition studies

One study assessed survival following successful hospital treatment of protein energy malnutrition in the Democratic Republic of Congo (formerly Zaire).[47] This study followed 171 children for 5 years after discharge and found that 18% died. The follow-up rate over this time was 76%. Mortality after 1 year was 10% indicating that most deaths occurred relatively early. While young age was predictive of post-discharge death (mean age of 26 vs. 59 months in dead and surviving children, respectively) neither weight-for-age, height-for-age, length of stay, or degree of hypoalbuminuria was associated with death at 1 year or 5 years following discharge.

Discussion

Thirteen studies that reported post-discharge mortality rates were identified. Studies varied in design, length of follow-up, location and in study population. The majority of studies were from African countries. In these studies we found a consistent trend of mortality rates similar to those seen in hospital. Of the six studies that reported both in-patient and post-discharge mortality, four reported mortality rates higher following discharge than during hospitalization.

The term "post-hospital syndrome" has recently been introduced and describes an acquired, transient period of vulnerability following discharge.[50] Not only does the acute (and sometimes chronic) illness contribute to derangements in normal physiologic function, other stressors such as sleep deprivation, poor nutrition, pain and adverse effects of medications contribute to a state in which the patient is more vulnerable to decline, even following recovery of the initial acute condition. Sepsis, the most common cause of death among children in developing countries,[36,51] is known to cause significant losses in adaptive immunity, perhaps contributing to the significant burden of post-discharge mortality observed.[52]

Ideally, all children discharged from hospital should be followed-up to ensure identification of children suffering re-emergence of an acute illness; however in an already over-burdened health system this is neither feasible nor cost-effective. Therefore, the identification of risk factors for post-discharge mortality is an important starting point for interventions aiming to reduce morbidity and mortality following discharge. In those studies which identified such risk factors, nutritional indicators (such as weight–for-age), young age, and previous hospitalizations as well as disease specific factors such as HIV infection and pneumonia were consistently associated with a poor prognosis following discharge. The only study identified which actively addressed post-discharge mortality built upon previous research indicating anemia was an important predictor of mortality after discharge. Unfortunately, however, the intervention of providing malaria prophylaxis did not substantially reduce 6 month post-discharge mortality. The timing of post-discharge deaths is also an important consideration since this may aid in determining the period during which post-discharge interventions should be applied. While the duration of follow-up varied significantly between studies (28 days – 5 years), the probability of death was

substantially higher during the first several months, indicating that post-discharge interventions during this period may offer the highest probability of success.

The integrated management of childhood illness (IMCI) program developed by the World Health Organization (WHO) is an attempt to compile the best available evidence for treatment of common pediatric diseases and facilitate the uptake of a standardized approach to these diseases in resource poor countries.[53] Even though significant focus of the IMCI has been placed on both inpatient and outpatient treatment there is a general lack of evidence based recommendations on the prevention of post-discharge morbidity and mortality. Formal recognition of the morbidity and mortality following hospital discharge, and its associated risk factors is required. The recent post-discharge surveillance study from Kenya analyzed the utility of identifying children with any one of several individual risk factors to determine the sensitivity and specificity of identifying children likely to die following discharge.[19] This study found that the presence of either low weight-for-age score, hospitalization greater than 13 days, hypoxia, bacteremia, hepatomegaly, or jaundice would identify 33% of discharges and 47% of post-discharge deaths. While this research can be used to better improve post-discharge care, significant numbers of deaths following discharge would still not be identified. Furthermore, limited resources for risk factor determination (such as blood culture) would make this process difficult to implement in many health centers throughout Africa. A new research approach specific to the identification of easily measured risk factors for use in a simple clinical prediction tool developed and validated for use in poorly resourced health centers could prove very useful. Furthermore, defining the population in whom such a prediction tool would be implemented in is also important as significant differences exist between patient groups to warrant different prediction tools (such as children with infectious diseases vs. children without infectious diseases). Once such tools are validated they could be incorporated into guidelines such as the IMCI to better improve post-discharge initiatives.

In addition to specific risk factors for, and timing of, post-discharge mortality, we also observed that in several studies many children who died did not die during a re-admission but rather died at home.[20,49] Although barriers to returning to hospital were not discussed in any of the studies, factors such as transportation costs, care costs and poor care may have contributed to this. Studies to identify specific barriers at the community level among parents of recently discharged

children could help drive effective interventions to improve health seeking behavior. Technological innovations such as the utilization of cellular technology may assist in identification of sick children in need of referral. Volunteer health workers have been utilized in a unidirectional manner (home-to-hospital) in many settings to identify children requiring community level treatment or referral to referral centers.[54] Use of these health workers for discharge referrals would decrease resources required for effective follow-up and referral in cases of disease emergence. Efforts by policy makers and global health funding organizations to overcome barriers such as these are required if health seeking behavior following hospital discharge is to improve.

One limitation of this review was that the studies that were identified often did not have post-discharge mortality as a primary outcome. It is therefore possible that other similar studies, further removed from the search terms used, were not identified. However, the systematic search utilized was intended to be sufficiently broad to identify most of such studies. Another limitation was that several studies had follow-up rates below 90%. It is unlikely, however, that the reported mortality rates would be lower since losses to follow-up likely represent a more vulnerable population with higher rates of post-discharge mortality. A further limitation was the lack of a valid quality scoring system. As most studies were not specifically designed to assess post-discharge mortality a scoring system based on general study features could also not be created. The reason was that most of the study features in various statements (CONSORT, STROBE etc.) are for determining validity for drawing specific inferences according to the objectives of the study. Presence (or lack) of these characteristics does not necessarily mean that inferences for post-discharge mortality estimates are good (such as blinding in an RCT).

Conclusions

Pediatric post-discharge mortality is a significant and generally unrecognized problem in developing countries. While several characteristics are strongly associated with post-discharge mortality, no validated tools are available to aid health workers or policy makers in the systematic identification of children at high risk of post-discharge mortality. Global health policy and research must focus on both the creation of tools to aid in defining groups of children most

likely to benefit from post-discharge interventions, formal assessment such interventions, followed by the scale-up of effective interventions.

Chapter 3. Selecting candidate predictor variables for the modelling of post-discharge mortality from sepsis: A protocol development project

Background

Acute Infectious diseases account for most childhood deaths in resource poor countries, particularly on the African Continent.[55] While the period of acute illness is well known to account for much of this burden, relatively little is known about the epidemiology of the post-acute period and its contribution to overall infectious disease associated mortality. A recent systematic review has found that the months following hospital discharge account for at least as many deaths as the hospital period.[56] Despite the apparently high burden of post-discharge mortality in children, little currently exists to address this important issue. The implementation of interventions to reduce post-discharge mortality must be preceded by robust research aiming to develop methods for identification of vulnerable children.[43] Such research protocols must ensure that the most important and relevant predictors are included for analysis in order to optimize model development.[57,58]

The method by which candidate predictors are selected vary widely among studies and many include informal discussions among the research team and colleagues or more formal methods such as focus group discussions, questionnaires and surveys. A well-recognized method by which groups can reach consensus on a subject of interest is the Delphi method.[59] The Delphi method is a structured communication technique in which a facilitator solicits experts to answer a questionnaire in two or more rounds. A summary of each round is reviewed by the experts providing opportunity to modify previously selected answers, thus converging, in theory, towards the most correct answer. This method has been used successfully in prediction modelling research as a means to generate a comprehensive set of candidate predictor variables to be used in statistical modeling.[60]

The purpose of this protocol development project was to generate a comprehensive list of candidate predictor variables for entry into a statistical model of pediatric post-discharge mortality, using a modified Delphi technique. Ultimately, the predictors derived will be used in the creation of post-discharge mortality prediction models.

Methods

Design

A modified two-round Delphi process was undertaken to determine an optimal set of candidate predictor variables to be collected for the prediction modelling portion of the study. As the primary aim of this project was to aid in protocol development, this did not satisfy the definition of research at the University of British Columbia and therefore was exempt from review from the research ethics board.

Participants

Participants in the Delphi process were recruited by the solicitation of the primary research team, and included both those solicited by the research team as well as the research team itself. The research team included experts in global health, critical care, pediatrics, statistics, methodology, epidemiology, computer engineering and infectious diseases. Expertise was sought in at least one area potentially relevant to post-discharge mortality. The required areas of expertise identified included (1) pediatrics, (2) sepsis, (3) infectious diseases, (4) microbiology/laboratory medicine, (5) international health, (6) epidemiology or (7) social sciences. The participants were invited to participate in both rounds of the Delphi process. Our target sample size was 20 individuals that covered all seven areas of expertise and included participants from the proposed research country (Uganda).

Process

The modified Delphi process occurred between November 2010 and January 2011 and was completed during two rounds of emailed surveys using SurveyMonkey® software (Palo Alto, CA). Fourteen days was granted to participants during each round of the process. After each round the research team members involved in candidate variable selection discussed the survey responses and determined whether the existing or suggested variable should be added, modified or eliminated. A final consensus of candidate predictors was made by the research team following the results of the second survey

Round 1

Round 1 of the Delphi process was initiated in November, 2010. An initial list of 17 candidate variables was generated by the research team prior to this first round of the Delphi process, following a review of existing literature as well as the clinical and research experiences of co-investigators (**Table 3.1)**. This list of 17 variables included multi-part variables (eg. vital signs labelled as a single variable although it included respiratory rate, temperature, heart rate and blood pressure). Therefore, the actual list of candidate variables for statistical modelling would be higher than the list of variables reviewed. Critical domains of the initial variable selection included (1) its potential as a predictor and likely inter-and intra-rater reliability of its measurement, (2) its general availability in most resource poor contexts, (3) its cost, and (4) the time and resources required collecting the variable. These four domains, therefore, were the primary component of the Delphi evaluation.

In addition to the rating of each of the 17 variables according to the four domains, participants were given the opportunity to make comments and suggest additional variables for consideration during the second round of the Delphi process. The primary research team considered each proposed variable and eliminated those variables deemed to be unsuitable based on any of the domains or if redundant (**e.g.** Nutrition status was available as weight/height for age z-score). The new set of potential candidate predictor variables were then incorporated into the second round of the Delphi process. Using the survey results from this initial round, the primary research team also modified or removed variables from the initial list of 17 candidate variables to be used in the final list of candidate predictor variables.

Round 2

The second round of the Delphi process was conducted in December, 2010. During this round 16 new variables were assessed using the same domains and scoring system used during the first round. The ability to make comments was preserved. This round did not include a re-review of the initial variables used during the first round. Using the results from this second round of evaluation, the primary research team retained, modified or removed the additional candidate predictor variables and incorporated these into the final list of candidate predictor variables.

Analysis

Evaluation of each variable was considered for applicability on 4 domains. These four domains included the applicability of candidate variables as (1) a potential predictor, (2) an available predictor, (3) a cost-effective predictor (4) a time/resource-effective predictor. The responses were meant to be specific to a resource poor context. Respondents scored each predictor as having either (1) high, (2) moderate, (3) unlikely or (4) no applicability for each of the four domains. Responses were tabulated and reported using descriptive analyses only (SAS 9.3, Carey, NC). The proportion of respondents indicating a high level of applicability was of primary interest. The proportion of respondents indicating unlikely or no applicability of the candidate variables to each domain was also of interest. A final list of variables for inclusion as candidate predictors was determined by the study team using both the results of the distributed survey results as well as other considerations (budgetary, research staff availability, equipment availability etc.).

Results

Twenty three participants from both resource rich and resource poor environments participated during the first round of the Delphi process. During this round, 17 initially proposed candidate predictors (**Table 3.1**) were evaluated and a further 40 were proposed. Of the 40 proposed variables, 16 were selected for inclusion in the second round. During the second round, 12 participants (52%) of the initial 23 completed the survey.

Round 1

Self-identified areas of expertise among the participants include pediatrics (70%), sepsis (57%), infectious diseases (30%), international health (26%) epidemiology (22%), critical care (17%), microbiology or laboratory medicine (9%) and the social sciences (9%). Participants included individuals from both high resource and resource poor countries.

Applicability of proposed candidate predictors as potential predictors

Of the 17 variables evaluated during this first round of the Delphi process, Oxygen saturation, height/weight, co-morbidities, age, maternal education and wealth received scores of "high

applicability" for over 80% of participants who evaluated these indicators (**Table 3.2**) Vital signs, vaccination status, length of stay, admission diagnosis, discharge against medical advice, and distance from hospital received a moderate amount of "high" ratings (60% – 80%). Sex, zinc level, hemoglobin level, and prior antibiotic use received low levels (<60%) of high ratings relative to the other variables. Zinc level in particular received few high ratings (29%). Although wealth received a high proportion of high ratings, only 13 participants rated this. Many respondents commented on their lack of knowledge of wealth scoring tools. Variables exhibiting the highest proportion of "unlikely" or "not at all" applicable included zinc level and sex, with 21% and 24% or participants providing these scores, respectively.

Applicability of proposed candidate predictors for availability

The availability of variables in a typical resource poor context was evaluated for each of the 17 candidate variables (**Table 3.3**). Variables scoring over 80% included length of stay, age and sex. Vital signs, height and weight, discharge against medical advice, co-morbidities, maternal education and distance were considered highly available by 60 – 80% of participants. Prior antibiotics, hemoglobin, zinc level, hemoglobin, zinc level and wealth was considered to be highly available in 40 – 60% of participants. Oxygen saturation, blood culture and immunization status was considered highly available in fewer than 40% of subjects. Only blood culture and vaccination status was considered unlikely or not available for more than 20% of participants.

Applicability of proposed candidate predictors for cost

The cost of obtaining candidate predictors was assessed (**Table 3.4**). Age and sex was noted to be highly applicable in terms of cost for greater than 80% of participants. Height and weight, length of stay, co-morbidities, admitting diagnosis, discharge against medical advice, maternal education, wealth and distance were all considered to be highly applicable in terms of cost in 60% – 80% of participants. Vaccination status, prior antibiotic use and hemoglobin were considered highly applicable in terms of cost in 40 – 60% of participants and oxygen saturation, blood culture and zinc level were all considered highly applicable in terms of cost for fewer than 40% of subjects. Twenty nine percent of respondents believed blood culture to be unlikely or not applicable in terms of cost and 78% of participants believed that zinc level was unlikely or not applicable in terms of costs.

Applicability of proposed candidate predictors for time and resources required

The applicability of time and resources required to measure each potential candidate predictor was assessed and closely mirrored the cost domain results (**Table 3.5**). The primary difference is that discharge against medical advice and the assessment of co-morbidities were rated highly applicable in 40% - 60% of participants in this domain rather than over 60% in the cost domain. Only zinc was associated with a high proportion of participants selecting it as being unlikely or not applicable (71%).

Proposed new variables

Forty additional variables were proposed as potential candidate predictors, many of which were similar or overlapping (**Table 3.6**). Sixteen of these were included in the second round of the Delphi process.

Round 2

Twelve participants completed this final round of the Delphi process. During this process 16 potential candidate predictor variables (or groups of predictor variables) were evaluated using the previously used domains and scoring system.

Applicability of proposed candidate predictors as potential predictors

Mental status was deemed to be highly applicable as a potential candidate predictor variable in 80% of participant responses, and was the highest of all 16 candidate predictors (**Table 3.7**). Urinary frequency prior to admission, duration of illness prior to admission, prematurity, glucose level, and acidosis measurement were considered highly applicable in 60% - 80% of responses. Previous hospitalizations in the past year, maternal co-morbidities and the number of parents living at home were associated with a high level of applicability in 40% - 60% of participants, while the time since last hospitalization, mid-upper arm circumference, presence of sibling deaths, blood coagulation profile, renal function profile and maternal age were all associated with fewer than 40% of participants considering them as highly likely to be associated with post-discharge mortality. Only maternal age and the number of parents living at home was considered to be unlikely or not at all applicable as predictors by more than 20% of participants.

Applicability of proposed candidate predictors for availability

The perceived typical availability in a resource poor context was evaluated for each of the newly proposed candidate predictor variables (**Table 3.8**). Duration of illness prior to hospitalization and mental status were considered highly available by over 80% of participants. Previous hospitalizations, maternal age, the number of parents living at home, bednet use and water source were considered highly available in 60% - 80% of subjects. Urination in 12 hours prior to admission, prematurity, sibling deaths, and glucose were considered highly available by 40% - 60% of participants, while the number of siblings, blood coagulation profile, acidosis measurement, maternal co-morbidities, renal function and mid-upper arm circumference were considered highly available in fewer than 40% of participants. Several candidate predictors were considered unlikely or not to be available by more than 20% of participants, including the number of parents living at home, maternal age, number of siblings, renal function, blood coagulation and acidosis measurement.

Applicability of proposed candidate predictors for cost

The proportion of participants rating the candidate predictor variables as highly cost-effective was over 80% for bednet use only (**Table 3.9**). Urination in the 12 hours prior to admission, previous hospitalizations, sibling deaths, number of siblings, maternal age, number of parents living at home and water source were considered highly cost-effective for 60% - 80% of participants, while time since last hospitalization, prematurity, maternal co-morbidities and glucose were considered cost-applicable by 40% - 60% of participants. Duration of illness prior to admission, mid-upper arm circumference, acidosis measurement, blood coagulation profile and renal function received a high applicability rating in terms of cost by fewer than 40% of participants. The laboratory variables including renal function, blood coagulation profile, and acidosis measures were considered unlikely or not applicable in terms of cost in over 20% of participants, as was collection of maternal age and the number of parents living at home.

Applicability of proposed candidate predictors for time and resources required

The responses of the participants for the applicability of the time and resources required to collect the proposed candidate predictor variables mirrored the results of the applicability of the cost of collection of these variables on all descriptive terms (**Table 3.10**).

Final list of candidate predictor variables

The final list of candidate predictor variables was determined through discussions among the primary research team (**Table 3.11**). Budget considerations and actual availability at the proposed research site played the most significant role following a review of the survey results. The final list of 30 candidate predictors was approved by the primary research team and incorporated into the research proposal.

Discussion

A list of candidate predictor variables was derived using a modified, 2-round, Delphi approach. This approach, utilizing the expertise of individuals not part of the primary research team, added considerable depth to the evaluation of candidate predictor variables, as evidenced by contrasting the initial list of predictors with the final list of predictors (**Tables 3.1 and 3.11**).

The final list of candidate predictors was chosen based on both subjective considerations by the research team and objective results of the survey. Some proposed variables that scored relatively poorly during the second round of the Delphi process were chosen based on very practical considerations at the research site. For example, mid-upper arm circumference was not highly rated on any of the domains. However, this variable was chosen as a simpler method of nutritional status than a measure based on the variables of height, weight and age. The true cost considerations from a research perspective included the cost of scales and length boards for height and weight, compared to a mid-upper arm circumference tape, which is less expensive. The research team, did however, agree with the results of newly proposed laboratory variables, which tended to score poorly in all domains, particularly in the cost and resources domains.

This protocol development project actively utilized experts from resource poor countries, beyond those on the research team, who had in-depth knowledge of current practices and standards at the

proposed research areas. This broad expertise ensured that the more pragmatic indicators were appropriately evaluated and further ensured that the overall context was broadly considered throughout the two phases of the Delphi process.[61]

This process was subject to several limitations. A primary limitation to this process was the inability to revise responses based on a summary of group responses. Because of this we were not able to evaluate more the effect of further consideration of individual responses. Further, no opportunities were available for specific discussion on any candidate predictor variables. Although provisions for comments were incorporated into the survey, these were only seen by the primary research team. The reason for this Delphi process simplification was to facilitate participation, rather than due to an accidental omission of this process. A further limitation of this survey was a relatively high proportion of individuals not completing the second round (10 out of 23). No identifying information or participant characteristics were collected during the second round of the survey and therefore the breakdown of self-identified expertise was not considered in the responses, as it was during the first round. However, each section of the survey (clinical, laboratory and social/demographic) was initiated by a question about the participants ability to contribute meaningfully and they were provided with an option to skip the section if they desired.

In conclusion, this modified Delphi process was an effective method to add both objectivity and to broaden the perspective for the selection of candidate predictor variables. This increases the likelihood that a robust set of candidate variables will be included in the proposed post-discharge mortality modelling research project.

Chapter 4. Post-discharge mortality in children with acute infectious diseases: Derivation of post-discharge mortality prediction models

Background

Acute infectious diseases continue to be the most important contributor to the 6 million children younger than 5 years who die every year, particularly in Africa.[55] It is widely accepted that as a global community we have fallen short in reducing under-5 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.[3] 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.[56] 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 is a city of approximately 85,000 and 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 the hospital associated with the Mbarara University of Science and Technology and is a primary training site for its health care graduates. The pediatric ward of MRRH admits approximately 5000 patients per year. The Holy Innocents Children's Hospital (HICH) is a faith-based children's hospital offering subsidised 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). 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 previously enrolled were excluded.

Study procedure

Following enrollment, a research nurse obtained and recorded clinical signs including a 1 minute respiratory rate, blood pressure (automated), axillary temperature, Blantyre coma score, and using the Phone Oximeter,[62] 1 min 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.[63] 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 Flemming et al.[64] The age corrected z-scores for systolic blood pressure were calculated using subjects' height, according to the procedures previously described.[65]

A blood sample was taken for measure of hemoglobin, HIV and a malaria blood smear (microscopy). HIV status was determined using rapid diagnostic test serial algorithm. All positive tests were confirmed by a separate test. 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 2 and 4 to determine the vital status of the child. Families with no telephone access received in-person follow-up by a field officer. At approximately 6 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.[66] 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 2-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.[67]

Outcomes

The primary outcome was post-discharge mortality at any time during the 6 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%. However, funding was insufficient to increase enrollment to 2000 subjects 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.[68] Following univariate analysis candidate models were generated using a step-wise selection procedure minimizing Akaike's Information Criterion (AIC). All models generated in this sequence which had an AIC value within 10% of the lowest value were considered as reasonable candidates. Missing data was imputed using multivariate imputation by chained equations.[69] 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. This was done to increase application in a variety of settings were the absence of certain key variables may occur.

Results

During the period of study 1824 subjects were screened for eligibility, of which 517 (28%) were excluded. Reasons for exclusion included isolated malnutrition (n=192), re-admission of 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=167). 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 65 (5.0%) subjects died, and 1242 (95.0%) were discharged alive (**Figure 4.1**). 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. 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 4.1**).

Post-discharge mortality

During 6 months of post-discharge follow-up 61 children died. 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 4.2**). 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, duration of illness prior to admission and time since last hospitalization. Time since last hospitalization was collected as an ordinal variable with 5 levels (<7d, 7-30d, 30-365d, >365d and never). This variable was treated as continuous in the analysis for reasons of parsimony and overall fit. 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 model

One primary model and 3 alternate models of equal sensitivity were developed for the prediction of 6-month post-discharge mortality (**Table 4.3**). The alternate models were developed while systematically excluding oxygen saturation, mid-upper arm circumference and HIV status, respectively, since these may not be routinely available in all clinical settings. The primary model included mid-upper arm circumference (mm), oxygen saturation at admission (percent), time since previous hospitalization, abnormal Blantyre coma score, and HIV status. The area under the receiver operator characteristic curve was 0.81 (95% CI 0.75 – 0.87) (**Figure 4.2**). At a probability cut-off of 0.035, this model had a sensitivity of 80% (95% CI 70 – 90) and a

specificity of 65% (95% CI 62 – 68). In a population similar to this model derivation cohort we would expect the positive predictive value to be 10.7%, and the negative predictive value to be 98.4% (**Table 4.4)**. The final model equation for the primary model was: logit(p) = 7.85 + (-0.047; mid-upper arm circumference at admission in millimetres) + (-0.041; SpO2 at admission as percent) + (-0.28; time period since last hospitalization) + (0.98; HIV positive) + (0.88; Blantyre coma score less than 5).

Model 2 excluded oxygen saturation (**Table 4.3**). 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). At a probability cut-off of 0.037 this model had a sensitivity of 80% (70 – 90) and specificity of 65% (95% CI 62 – 67) and would generate a positive and negative predictive value of 10.7% and 98.6%, respectively, in a population similar to the derivation cohort.

Model 3 excluded mid-upper arm circumference (**Table 4.3**). The final model included oxygen saturation, time since last hospitalization, HIV status, abnormal Blantyre coma score, weight-for-age z-score and age. The area under the ROC curve for this model was 0.80 (95% CI 0.74 – 0.86). At a probability cut-off of 0.031 this model had a sensitivity of 80% (70 – 90) and a specificity of 58% (95% CI 55 – 61). The positive and negative predictive values were 9.1% and 98.1%, respectively.

The fourth and final model excluded HIV status and included mid-upper arm circumference, oxygen saturation, time since last hospitalization and the Blantyre coma score (**Table 4.3**). This model had a final area under the ROC curve of 0.80 (95% CI 0.74 – 0.86) and with a probability cut-off at 0.034 achieved a sensitivity of 80% (95%CI 70 – 90) and specificity of 62% (95% CI 59 – 65). The positive and negative predictive values were 9.9% and 98.3%, respectively.

An attempt to develop a model that did not use any anthropometric variables was not successful as no candidate model achieved specificity greater than our pre-defined threshold of 50% while maintaining acceptable levels of sensitivity. This underscores the importance of malnutrition as the most important predictive variable for post-discharge mortality.

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, abnormal Blantyre coma score, time since last hospitalization, HIV status, weight and age. Four prediction models were developed to ensure its effective application in a variety of clinical circumstances when certain variables may not be available (specifically, oxygen saturation, HIV and mid-upper arm circumference). 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 would be identified and that only one-third of admitted children would require intervention. These children have an average mortality risk of approximately 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.[41] 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 show to improve care in the regions where it has been implemented.[70] 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 the 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. 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.[71–73]

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, and where mid-upper arm circumference was not used, weight-for age z-score played a major role. 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.[19,34,46] 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. This appears to promote a vicious cycle of infection and malnutrition. While this is very difficult to address, a focus on nutrition (micronutrient and macronutrient) both 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. Promotion of good health behavior 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 a 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.[7] 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.

Conclusions

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.

Chapter 5. Pediatric post-discharge mortality in Uganda: A prospective cohort study

Background

Although substantial gains in child-mortality reduction have been seen in many areas of sub-Saharan Africa, most countries within this region will not achieve the required two-thirds reduction target by the end of 2015 as outlined at the Millennium Summit of 2000.[1] While deaths from infectious diseases such as diarrhea, malaria and pneumonia have reduced significantly, infectious diseases still account for most under-5 deaths in Africa.[3] Improvement in acute care and access to health facilities have been the focus of many interventions across Africa, resulting in improved outcomes for these common diseases.[55,74] Improved coverage of preventative interventions such as the use of insecticide treated mosquito nets, essential immunizations and clean drinking water have also been credited with decreases in child mortality.[75]

Despite this progress, a vulnerable group that continues to be neglected are those children who have survived severe episodes of acute infectious diseases. Studies have shown that children in the post-discharge period are particularly vulnerable, often experiencing mortality rates as high as those who are hospitalized.[56] The discharged child, therefore, represents an easily identified population in which follow-up intervention could have a profound impact on child mortality. As access to health centers increases throughout many areas of sub-Saharan Africa, interventions in children being discharged could represent an increasingly effective method in decreasing child mortality. Interventions to reduce post-discharge mortality, therefore, represent an important area of policy and research that must be facilitated. The confirmation of previously identified risk factors and the further characterization of risk will fill gaps in the understanding of this issue and, more importantly, the development of new interventions.

Current estimates of post-discharge mortality, and its associated risk factors, are often limited by retrospective study designs or poor follow-up rates.[19,23] Randomized controlled trials conducting post-discharge follow-up have been done but are limited by the interventional nature of the studies which may have influenced outcomes following discharge.[22,33] Further, studies are often disease specific (malaria, pneumonia, diarrhea etc.) limiting their generalizability.[21,33,46] This is especially problematic due to the inherent difficulty in establishing a gold standard for these diagnoses, and the often occurring issue of co-infections and co-morbidity. An easily identified,

and relevant, dichotomy among hospitalized (and discharged) children is whether or not the illness is secondary to a suspected or confirmed infectious disease. This easily applied stratification is especially relevant in the resource poor context where most hospital admissions are secondary to infectious diseases, and where these diseases are major contributors to both in hospital and out of hospital mortality.

Currently, no prospective cohort studies of post-discharge mortality on children with suspected or proven infections have been published. The purpose of this study was to describe the outcomes of children admitted with a proven or suspected infectious disease following hospital discharge.

Methods

Population

This study was conducted at two hospitals (The Mbarara Regional Referral Hospital and The Holy Innocents Children's Hospital) in Mbarara, Uganda. 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 the hospital associated with the Mbarara University of Science and Technology and is a primary training site for its health care clinicians. The pediatric ward of MRRH admits approximately 5000 patients per year. The Holy Innocents Children's Hospital is a faith-based children's hospital offering subsidised fee-for-service outpatient and in-patient care in Mbarara. The HICH admits approximately 2500 patients per year.

Design

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

Eligibility

All children aged 6 months to 5 years who were admitted with a proven or suspected infection were eligible for enrollment. Subjects previously enrolled were excluded.

Study procedure

Following the admission of an eligible child, parents were counselled about the study and were provided an opportunity to consent to the enrollment of their child. Immediately following enrollment, a research nurse obtained and recorded clinical signs including a 1 minute respiratory rate, blood pressure (automated), axillary temperature, Blantyre coma score, and using the Phone Oximeter, a 1 min photoplethysmogram (PPG), blood oxygen saturation (SpO_2) and heart rate.[62] Anthropometricc 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.[63] 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.[64] The age corrected z-scores for systolic blood pressure were calculated using subjects' height, according to the procedures previously described.[65]

A blood sample was taken for measure of hemoglobin, HIV and a malaria blood smear (microscopy). HIV status was determined using rapid diagnostic test serial algorithm. In this algorithm, positive tests are confirmed by a separate test (from a different manufacturer) and ties are broken with a third test (from a third manufacturer). Children under 12 months of age with a positive test were confirmed using PCR. Hemoglobin and leukocyte counts were measured on a Beckman Coulter Ac.T 5 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 2 and 4 to determine the vital status of the child. Families with no telephone access received in-person follow-up by a field officer. At approximately 6 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.

Outcomes

The primary outcome was post-discharge mortality during the follow-up period. The secondary outcome was the composite of post-discharge mortality or re-admission.

Analysis

The primary outcome of post-discharge mortality and the secondary outcome of post-discharge re-admission or mortality were plotted using the Kaplan-Meier method. The association of each variable with time to the primary outcome of post-discharge mortality and the secondary outcome of mortality or re-admission was assessed using Cox regression. By fitting these models we obtained log hazard ratios for each variable, which were exponentiated to produce hazard ratios. We used the log likelihood ratio test to assess the significance of the associations represented by the models. The significance of each regression estimate was tested by the Wald statistic.

Because of the large number of variables, few primary outcomes and the significant multicollinearity between many variables, an adjusted model using independent variables in their original form was not ideal. Principal component analysis was therefore conducted to reduce the number of variables and eliminate correlation between independent variables. Since the raw variables represented continuous, ordinal and nominal data, the PRINQUAL procedure in SAS[76] was used to transform the data to make it suitable for principal component analysis. The algorithm attempts to find transformations for each variable such that the total variance explained by the first *r* principal components is maximized. Nominal variables were transformed using an optimal scoring technique (OPSCORE), ordinal variables were transformed using the MONOTONE transformation and continuous variables were transformed using an MSPLINE transformation. Principal components were then extracted from the correlation matrix using the

FACTOR procedure in SAS. Orthogonal rotation (Varimax) was performed to generate a rotated factor pattern for improved interpretation of the loadings of each component. Principal component loadings of greater than 0.30 were considered significant and variables meeting this level of significance were used in the interpretation of the principal components. Only those principal components with eigenvalues of greater than 0.1 were eligible for inclusion in the multivariable model.[77] Eligible principal components were entered into a univariate cox proportional hazards model. Those with p-values of less than 0.1 were retained and included and reported in a multivariable Cox model. Results were interpreted according to their level of significance only and not their regression coefficients.

Sample size

This study was designed for dual objectives. The first was to derive clinical prediction models for in-hospital and post-discharge mortality (for publication elsewhere) and the second was to describe the epidemiology of post-discharge mortality. The sample size was determined primarily for the former project. Briefly, to optimally derive a prediction model we aimed to enroll 1000 subjects assuming an outcome rate of 10% for both in-hospital and post-discharge mortality. An interim analysis showed that the in-hospital and post-discharge mortality rates were approximately 5%. Funding allowed enrollment to increase to 1307 subjects.

Results

During the course of the study, 1307 subjects were enrolled out of 1824 subjects who were screened for eligibility. Reasons for exclusion included isolated malnutrition (n=192), re-admission of enrolled subject (n=51), refusal of consent (n=22), cardiac disease (n=19), poisoning/drug reaction (n=19), cancer (n=12) and a range of other non-infectious admissions (n=167). During the course of admission 65 (5.0%; 95% CI 3.8% - 6.2%) subjects died, and 1242 (95.0%) were discharged alive (**Figure 5.1**). The median length admission for enrolled children who were discharged was 3 days (IQR 2 – 5 days). Six children (0.5%) were lost to follow-up and a further 15 children (1.2%) received partial follow-up (defined as less than 150 days of follow-up). The remaining 1221 children (98.3%) received full post-discharge follow-up.

Post-discharge mortality and re-admission

During the post-discharge period 61 children died (4.9%; 95% CI 3.7% - 6.1%) (**Figure 5.2**). The median time to death of those who died was 30 days (IQR 7 – 81 days). Of the 61 deaths, 41 (67%) occurred outside of a hospital and 20 (33%) occurred during a hospital re-admission. During the post-discharge period 204 (16.5%) children experienced at least 1 re-admission (**Figure 5.3**), of whom 20 died (9.8%). The composite outcome of re-admission or death occurred in 245 (19.8%; 95% CI 17.5% - 21.9%) children. The median time to re-admission or death of those suffering an event was 59 days (IQR 25 – 106 days).

Malnutrition and post-discharge mortality/re-admission

Underweight (weight for age z-score less than -2), wasting (weight for height/length) z-score less than -2) and stunting (height/length for age z-score less than -2) were common, affecting 28%, 34% and 28% of children, respectively (**Table 5.1**). Malnutrition, as defined by a mid-upper arm circumference measurement of less than 125mm was also common, affecting 17% of children. All anthropometric measures were associated with increased hazards of post-discharge mortality but were not consistently associated with an increase in the hazard of the composite of re-admission and death. The strongest risk factor for post-discharge mortality was a mid-upper arm circumference of less than 115mm (a standard cut-point for severe malnutrition), conferring a hazard ratio of 9.74 (95% CI 5.71 – 16.61) compared to the reference category of a mid-upper arm circumference of greater than 125mm (**Table 5.2**). The range of 115 – 125 mm mid-upper arm circumference (moderate malnutrition) was associated with a lower, but statistically significant hazard ratio of 2.66 (95% CI 1.16 – 6.08). Severe underweight status (weight for age z-score of less than -3) was associated with a hazard ratio of 4.58 (95% CI 2.67 – 7.85) and moderate underweight status of -2 to -3 with a non-statistically significant hazard ratio of 1.65 (95% CI 0.75 - 3.61), compared to the reference of a weight for age z-score of greater than -2. Both stunting (length/height for age z-scores) and wasting (length/height for weight z-scores) were associated with statistically significant increases in post-discharge mortality hazards, with both levels (less than -3 and -3 to -2) showing hazard increases of approximately 2.5 fold. Of all the anthropometric variables, only mid-upper arm circumference of less than 115 was associated

with statistically significant increases in the hazard of death or re-admission, HR 1.83 (95% CI 1.25 – 2.68).

Clinical signs

Clinical signs at admission included heart rate, blood pressure, respiratory rate, temperature, oxygen saturation and Blantyre coma score. In the univariate analysis only temperature, oxygen saturation and Blantyre coma score (dichotomized as normal and abnormal) were significantly associated with post-discharge mortality. Only oxygen saturation was associated with the composite of mortality or re-admission. With a reference of >95% saturation, those with oxygen saturation measures of less than 90% had a hazard ratio of post-discharge death of 3.23 (1.71 – 6.10) and post-discharge death or re-hospitalisation of 1.47 (95% CI 1.10 – 1.98). An oxygen saturation of between 90 and 95% was not associated with death or the composite of death or re-hospitalization. An abnormal Blantyre coma score was associated with a hazard ratio of 2.35 (95% CI 1.28 – 4.34) for the outcome of post-discharge mortality but was not significantly associated with the composite of mortality or re-admission, HR 1.19 (95% CI 0.81 – 1.74). In the univariate analysis temperature was divided into 4 categories. Hypothermia was defined as less than 36 degrees Celsius, normothermia was defined as 36 – 37.5 degrees, and hyperthermia was divided into 37.5 – 39 and greater than 39 degrees Celsius. Using these categories, only hypothermia was associated with post-discharge mortality with a hazard ratio of 3.31 (95% CI 1.15 – 9.53). No temperature categories were associated with the composite of mortality or re-admission. In the univariate analysis tachypnea, tachycardia and hypotension were not significantly associated with post-discharge mortality or the composite of mortality or re-admission.

Social and health behavior variables

Social and health behavior variables collected at admission included bed net use, maternal education, distance from hospital, maternal HIV status, maternal age, number of children in family, sibling deaths, water source and use of boiled water for drinking. None of these were associated with post-discharge mortality or the composite of mortality or re-admission.

Discharge diagnoses

The most common discharge diagnoses, as recorded by the treating physician, were pneumonia (n=390, 31%), gastroenteritis (n=96, 7.7%) and malaria (n=626, 50%). The most common co-morbidity was HIV (n=58, 4.7%). Parasitemia was present in 418 (34%) subjects. Admission hemoglobin as a measure of anemia was recorded with mild (10 – 11g/dL), moderate (7 – 10g/dL) and severe anemia (<7g/dL) present in 190 (15%), 376 (30%) and 331 (26.8%) of subjects, respectively. In the univariate analyses, pneumonia and HIV were associated with higher hazards of post-discharge mortality, HR 2.00 (95% CI 1.21 – 3.31) and 4.70 (95% CI 2.45 – 9.04), respectively, while malaria was associated with a lower hazard of mortality, HR 0.37 (95% CI 0.21 – 0.66).

Other variables

Other relevant variables collected included whether the admission was due to a referral, discharge against medical advice, length of stay, duration of illness, and time since last hospitalization, all of which were associated with post-discharge mortality. Discharge against medical advice was associated an increased hazard of mortality, HR 4.24 (95% CI 2.44 – 7.34), but was not significantly associated with the composite outcome of death or re-admission, HR 1.40 (0.93 – 1.59). Likewise, duration of admission of greater than 5 days (vs less than 3 days) was associated with a higher hazard of post-discharge mortality, HR 3.23 (95% CI 1.78 – 3.22) but not mortality or re-admission, HR 1.19 (95% CI 0.86 – 2.07). Time since the last episode of hospitalization was strongly associated with both post-discharge mortality and the composite of post-discharge mortality or re-admission. With the reference of no previous hospitalizations each category of time was associated with a lower hazard of the outcome as the duration increased. A hospitalization within the previous 7 days was associated with hazard ratios of 3.41 (95% CI 1.40 – 8.27) and 2.60 (95% CI 1.62 – 4.19) for post-discharge mortality and post-discharge mortality or re-admission, respectively. Re-admissions more than 1 year prior to the index admission were not associated with an elevated hazard of either outcome.

Principal component regression

Principal component analysis was conducted utilizing all 33 candidate variables. Of the 33 possible components, 32 had eigenvalues of greater than 0.1 and were therefore retained for use in the multivariate regression modelling procedure. Components 1 through 8 explained over 50% of the total variance. Components one (MUAC, weight for age z-score, weight for length/height z-score) and two (weight for age z-score and height for age z-score) represented nutritional status. The third component represented a combination of maternal age and the number of children in the family. The fourth component represented the number of siblings and sibling deaths. The fifth component contained MUAC and age while the sixth component included the diagnosis of clinical malaria and a positive blood smear (parasitemia). The seventh component was loaded with only pneumonia and the eighth component contained only the hemoglobin level.

Twelve of the 32 eligible principal components were retained and used in the multivariable component regression analysis based on their univariate association ($p<0.1$) with the dependent variable. In the multivariable Cox model, seven of the components remained statistically significant (**Table 5.3**). The variable loadings of these components largely reflected the results of the univariate analysis of the raw variables. Mid-upper arm circumference (alone and in combination with age), oxygen saturation, time since last hospitalization, Blantyre coma score, discharge against medical advice and HIV status were the variables with significant contribution in these seven components. Of the 12 components, only the first 3 (components 1, 2 and 5) were significantly loaded with more than 1 variable.

In the secondary outcome, only components 8, 12 and 17 were shown to be associated. Component 8 was loaded primarily with the hemoglobin variable and was only significant in the univariate analysis. The multivariate analysis showed components 12 and 17 to be statistically significant, reflecting the results of the analysis of the non-transformed variables.

Discussion

This is the first prospective study of post-discharge mortality among an infectious disease cohort of children in a resource poor context. Post-discharge mortality was a frequent outcome and reflects the general vulnerability of children during the post-discharge period. This vulnerability

appears to be secondary to the degree of illness at the time of admission, malnutrition, self-discharge and HIV co-infection.

Malnutrition was clearly defined as a key risk factor for post-discharge mortality, with each of the anthropometric measures producing high hazard ratios for this outcome. This has been previously observed.[19,34,46] In the multivariate model, however, the only components containing an anthropometric variable were components 5 (MUAC + Age) and 32 (MUAC only), suggesting that mid-upper arm circumference is independently more important than other measures of malnutrition as a risk factor for post-discharge mortality. This is very useful information as MUAC is both easier and less resource intensive to measure than weight for age, weight for height or height for age.

The severity of illness at admission, as defined by the combination of hypoxia, abnormal Blantyre coma score and hypothermia, was an important measure of risk. This is an important observation since it may otherwise be assumed that only the degree of recovery from illness is important.

The prominence of a prior admission and time since the last hospitalization in the multivariate models is evidence of a decreasing level of vulnerability over time, independent of the severity of illness recorded during the index admission. The survival curve of the enrolled children confirms that in this cohort, the risk of death does decrease over time. This was also shown in a study of all pediatric discharges in Guinea Bissau where the risk of death compared to community controls was highest initially but decreasing to community levels after 6 months.[20] This has important implications for post-discharge interventions as these must incorporate strategies that persist beyond the first several weeks.

In this study, most post-discharge deaths occurred outside of a hospital context. This is particularly concerning since it suggests that initial health seeking is often not followed by subsequent health seeking among those who are most vulnerable. A recent systematic analysis of severe respiratory infections in children found that while most episodes were treated in hospital, most deaths occurred outside of the hospital.[7] Although this study does not report the proportion of out-of-hospital deaths that occur during the post-discharge period, our results indicate that many of these deaths do occur in children who were first treated in the hospital.

Further, these results may explain the reason why risk factors for the composite of re-admission and mortality were not detected. Since most deaths occur outside of a re-admission, admission is unlikely to serve as a useful surrogate of recurrent severe disease since many cases of severe disease do not result in re-admissions.

This study is subject to several limitations. The low number of mortality outcomes observed limits the power of this study to detect potentially important associations between the independent variables and mortality, particularly for the social and health behavior variables. Losses to follow-up occurred infrequently and are therefore not likely an important cause of unobserved deaths. During the course of this study only 6 children were completely lost to follow-up and only 15 had partial follow-up. Finally, this study represents only the catchment of two hospitals in Southwestern Uganda and may not be representative of other resource poor areas in Africa. However, this study utilized the catchment populations of both a referral hospital as well as a mission hospital, providing some degree of diversity.

In conclusion, mortality following discharge in an important yet poorly recognized cause of under-5 mortality. Further research on the burden of post-discharge mortality on neonates, young infants and older children is urgently required to further characterize this issue among the broad pediatric population. Interventions aimed at decreasing post-discharge mortality must be prioritized in the continued effort to further reduce childhood mortality.

Chapter 6. Pediatric out-of-hospital deaths following discharge: A mixed methods study

Background

Of the 6.3 million deaths among children under age 5 years, over half occur due to infectious sources.[55] The leading causes of death among these children – pneumonia, diarrhea, and malaria – are directly or indirectly related to infections. Focus on infectious disease in Sub-Saharan Africa will become increasingly important, as the region is projected to account for 60% of all child deaths by 2030.[55]

Some studies suggest that child mortality due to infectious disease disproportionately occurs outside of the hospital context, rather than in the hospital. A recent systematic analysis of published and unpublished studies of severe acute respiratory infections in children under 5 years found that although most episodes (62%) were treated in the hospital, 81% of the deaths from severe respiratory infection occurred outside of the hospital context.[7] This study did not identify the proportion of out of hospital deaths which at some point received hospital care. This relationship is of critical importance since previous research has shown that among children who died following discharge, most do not successfully seek care at a hospital prior to death.[20] Post-discharge death in children is increasingly being recognized as a major contributor to overall child mortality.

A systematic review of pediatric post-discharge mortality found that rates of death after hospitalization often exceeded in-hospital mortality. Post discharge deaths generally occurred early (within several weeks of discharge) and in many cases did not occur in hospitals.[56] Several factors, including inadequate health seeking behavior and poor access to hospital care, are responsible for the high occurrence of out of hospital death.[7] Barriers to seeking care in Sub-Saharan Africa are complex and can include financial constraints, distance to health facilities, cultural practices, gender dynamics, limited knowledge or information, and health facility disincentives.[78,79] These barriers are thought to contribute to increased child mortality, for instance, living a long distance from a health facility increased mortality risk by 17% in Tanzania.[80]

Malnutrition, previous hospitalizations and HIV are often identified as key risk factors for post-discharge mortality.[56] While these risk factors may assist clinicians in the identification of vulnerable children, they represent only some of the many parameters necessary to both understand and prevent post-discharge mortality. Currently, little is known about the health seeking decisions made by caregivers following hospitalizations for acute illness. Further, the context surrounding out of hospital death has not been investigated in any research of post-discharge mortality. Improved understanding of the circumstances of post-discharge mortality and the barriers faced by caregivers is important for the development of interventions aimed at reducing this burden. The objective of this study is to evaluate the context surrounding out of hospital deaths in children recently admitted for an infectious illness and to determine the most important barriers to seeking timely care in children who died out of hospital.

Methods

Population

This study was conducted on a sub-set of participants of a larger cohort study focused on determining predictors of post-discharge mortality among children admitted with infectious illness. A detailed review of the methods has been described previously (**Chapter 5**). Briefly, all children aged 6 months to 5 years admitted to Mbarara Regional Referral Hospital (MRRH) and Holy Innocents Children's Hospital (HICH) with a suspected or confirmed infectious illness were eligible for inclusion into the main study. All enrolled children had baseline characteristics measured which included clinical, laboratory and social variables. Patients received routine care during admission and were subsequently followed-up at 6 months post-discharge for a brief questionnaire to determine health status and health seeking during the post-discharge period.

An interim analysis of this study suggested that most post-discharge deaths occurred outside of the hospital context. The study protocol was, therefore, amended to conduct detailed qualitative interviews with families of study subjects who died during this period. The purpose of these interviews was to gain further insights into the circumstances behind these out of hospital deaths and to determine the most important barriers to seeking hospital care during the post-discharge period from the caregiver's perspective.

Eligibility

All subjects who were enrolled in the primary study and who died outside of the hospital during the post-discharge period were eligible for re-enrollment and re-consent. This amendment was approved by the institutional review boards at the Mbarara University of Science and Technology in Mbarara, Uganda and the University of British Columbia in Vancouver, BC.

Study procedure

The families of eligible subjects who died outside of the hospital during follow-up were contacted by phone and invited to participate in this study. If verbal consent was obtained, the primary caregiver was visited at their home and formally re-consented. A research nurse trained in qualitative methods administered a structured questionnaire recorded using a digital audio recorder (**Table 6.1**). The questionnaire consisted of eight open-ended questions related to events leading up to the child's death and subsequent probes. Questions sought to explore health seeking behavior and barriers to care just prior to death.

Analysis

Interviews were translated and transcribed from Runyankole-Rukiga into English. Thematic codebook development followed a standardized framework.[81] Through an iterative process, interviews were coded and analyzed for descriptive and interpretive themes. Thematic frequencies were generated to quantify medical symptoms, health seeking behavior, and barriers to care. Common themes were summarized to describe conceptual frameworks elicited by caregivers.

To determine if the demographic, social or environmental factors reported at admission were associated with out of hospital death (vs. in-hospital death), univariate logistic regression analysis was conducted. Analyses were limited to univariate due to the relatively few outcomes available. All quantitative analyses were conducted using SAS 9.3 (Carey, NC)

Results

Participant characteristics

From the cohort of 1,307 children, sixty-one died within six months following discharge from the hospital, with the majority (n=40) dying outside of the hospital rather than in the hospital. Among children who died at home the majority had discharge diagnoses of malaria, pneumonia, HIV and/or anemia. For mothers, the mean age was 29 years, and 35 (87%) had either no formal education or only primary education (**Table 6.2**).

The participant population was also characterized by their home environment. Most caregivers (n=27, 67.5%) lived more than one hour from the hospital. For most, their water supply came from shallow wells, and approximately one-third of children always slept under a bed net.

Post-discharge mortality

Among 40 children who died following discharge, 31 (77.5%) were staying with both parents just prior to death. Over half of post-discharge child mortality occurred at home (n= 24, 60%), while another one-third (n= 11, 27.5%) on the way to or upon reaching a medical facility. The remaining children died at or on the way to church, to stay with family, or on the way home from the hospital.

Quantitative results

Several social and environmental factors influenced likelihood of death outside the hospital, rather than reaching the hospital (**Table 6.3**). Maternal education was significantly associated with odds of out of hospital death, such that those with post-secondary school education had a 96% lower odds of their children dying outside the hospital than those with only some or no primary school education (OR 0.04; 95% CI 0.00 – 0.59). The odds of the child dying outside the hospital decreased by 62% with each additional level of maternal education, from primary to secondary to post-secondary (OR 0.38; 95% CI 0.19 – 0.81). Of borderline statistical significance, children who lived more than 1 hour from the admitting facility had an odds ratio of 3.20 (95% CI 0.92 – 11.12).

Within the home environment, bed net use and water source were also associated with increased odds of death outside the hospital. Children who never used bed nets had much higher odds of out of hospital death than those who used bed nets (OR 8.00; 95% CI 1.56 – 41.03). Similarly, the odds of dying outside the hospital for children with a shallow well as their primary water source were 10.5 times the odds of those with municipal water as their primary source (OR 10.50; 95% CI 2.58 – 42.68). The sex, age, and HIV status of the child did not appear to be associated with out of hospital death, although the small sample does not rule out type II error.

Among children who died, the median duration of hospital stay during the initial admission was 4.5 days, with half of all deaths occurring within 30 days following discharge. Approximately one-third of caregivers (n=12, 30%) removed their child from the hospital against medical advice. However, leaving against medical advice was not associated with out of hospital death (OR 0.97; 95% CI 0.30-3.11).

Descriptive qualitative results

Common symptoms

Nearly all caregivers (n= 36, 90%) recognized that their child was increasingly sick prior to death. For many children, death occurred within 24 hours of the parent recognizing increased signs of illness (n=15, 37.5%). Though child illnesses varied widely, caregivers tended to notice similar symptoms just prior to death. Caregivers commonly observed that their child had increased weakness, difficulty breathing, cough, vomiting, fever, and severe pain. These descriptors highlight common symptoms and factors that are notable to caregivers.

Health seeking behavior

Almost all caregivers considered seeking care for their child prior to death (n=36, 90%), but a small minority did not consider additional care due to monetary expense, recent discharge from the hospital, or lack of previous improvement. One caregiver explained: “Since I had just been discharged from a big hospital, [I] did not think of seeking any other care.” Of the 36 caregivers who considered seeking care, only 30 caregivers actually did so. Common limitations included transportation costs and arrangements. Among caregivers who did not access care, the majority had children who died within 24 hours of noticeable symptoms. These caregivers reported, “If

the sickness was not sudden, they would have taken the child back to Mbarara… but it wasn't possible because the child died within a short time."

Most caregivers sought multiple means of addressing the child's illness, including home remedies, traditional medicine, health centers, hospitals, and divine intervention. Initial point of care, indicating the first care seeking behavior after noticing symptoms, varied among caregivers. The majority first sought care at hospitals (n=11, 27.5%), with a smaller minority initially going to health centers (n=10, 25%) or utilizing traditional medicine (n=7, 17.5%). When people took their child to traditional healers or herbalists but noticed no improvement, they then turned to hospitals or health centers for healing. For example, one caregiver said: "Child was taken to the herbalist who excised the enlarged lymph nodes and gave herbs for the enlarged spleen. I noted no improvement, [so] decided to take him to the nearby health center." All children who accessed care but died within 24 hours of noticeable symptoms sought help from a hospital or health center, not traditional medicine. Most of these children died at, or on the way to, a medical facility due to sudden onset of symptoms.

Common barriers to care

Financial constraints were the most common barrier to seeking care at a medical facility. This barrier often presented as limited transportation options, which became particularly important when the child's health deteriorated during the night. Lack of paternal support also played a significant role in financial instability for some caregivers. When recently discharged, some caregivers did not perceive the need to return or assumed their child did not need further treatment. Most notably, if a caregiver did not observe their child improving after one or multiple visits to a medical facility, they were less likely to return just prior to the death of their child. Approximately one-third of caregivers (n=15, 37.5%) reported no barriers to seeking care at a medical facility (**Table 6.4**).

Though many barriers were mentioned, two responses were commonly given when asked if anything could have been done to help the child. Caregivers focused on the need for affordable transport options and access to improved health care services. One father said "if they had fast means to take their child to hospital, maybe the child's life would have been saved." Distance and road infrastructure contributed to limited transport, as one mother described, "the road was

so flooded that she failed to get means to reach the hospital in time." In addition, caregivers often felt access to better health care – through more services or larger medical centers – would have helped their child, wishing they had "the money to take [their child] to bigger hospitals for more tests."

Interpretive qualitative results

Role of important others

Few children were seen by members of the village health team (VHT) prior to death (n=6, 15%). Of those who were visited, the VHT served the role of referring to the hospital or providing medication. Some caregivers noted there was not a VHT in their community. More often, caregivers had "important others" with whom they sought advice on their child's health. These individuals or groups were influential to the caregiver's health seeking behavior. Over one-third (n=16, 40%) of caregivers sought advice from neighbors or local health care workers. Others turned to local leaders, family, religious congregations, and traditional healers for advice. All health care workers referred the caregiver to a hospital for care, while neighbors more commonly recommended herbal or traditional medicine. The consistency and influence of important others indicates they are a salient contributor to health seeking behavior.

Role of the hospital experience

The in-patient experience reportedly had some influence on post-discharge mortality and health seeking behavior. Though not asked explicitly, approximately one-third of caregivers reported that their child was initially discharged from the hospital while still sick and exhibiting symptoms, such as vomiting, diarrhea, severe weakness or convulsions. Among those who returned to a health facility prior to death, some felt the hospital failed to effectively care for their child, while others indicated the health care workers tried their best. Interestingly, negative in-patient experiences did not always color overall perceptions of the health care provided. For one family, they described how the "process of referral was delayed by health workers… [and] during this time the child's condition continued to worsen (convulsing and started bleeding through the nose and mouth)." However, they felt that "the health workers in the hospital did their best and gave all possible care."

In certain instances, following medical advice seemed to delay health seeking behavior post-discharge. Some caregivers said recent care/discharge or an impending follow-up appointment delayed them from returning, even when their child's symptoms worsened. For example, one caregiver explained: "the child developed difficulty in breathing, sharp pains and was complaining of thirst… [but] they thought the child would become better since she was on medication they were given at discharge from the hospital." Though symptoms were present, they were discounted or considered likely to improve or not recognized as severe enough to seek immediate care.

Acceptance of child mortality

Many caregivers expressed acceptance of their child's death. Half of all caregivers (n=18, 45%) said nothing could have been done to help their child. These caregivers commonly mentioned that the illness was "incurable". Solace seemed to come from the belief that all avenues of care had been pursued. Caregivers noted that "all the possible measures and assistance were given by both the health workers and the neighbors." Many tended to focus on what had been done for the child, rather than what could have been done, especially if additional measures were unavailable. Through various expressions, caregivers stated that "[their child] died a natural death like any other person can die."

Notably, religion seemed to play a dichotomous role as both curative prior to death and consoling following death. Some caregivers took their child to church or religious leaders for prayers, as a means of addressing their illness. One caregiver felt that, "if the child had been taken to a prayer palace in Kampala, he would have survived." Others used a religious framework to explain their child's passing. Many noted that "it was God's Plan that [their child] pass on at that time." To cultivate acceptance, caregivers often focused on the actions taken to help the child and acknowledged "the rest was God's Plan."

Discussion

This study examined the context of post-discharge deaths occurring outside of a hospital and determined important barriers to seeking timely medical care in critically ill children during the post-discharge period. We found that most caregivers pursued multiple avenues of care for their

child, but in many cases, the child's health deteriorated quickly. Common barriers, such as limited transportation and monetary constraints, delayed care seeking prior to death. For recently discharged children, the caregivers often expressed hesitancy to seek immediate care. Many perceived upon leaving the hospital that the child was cured or on trajectory for recovery, even with persisting symptoms. Recognition of preliminary symptoms or improved modalities of reaching care could enable earlier heath seeking behavior.

These interviews also demonstrated that health care access extends beyond resource limitations; this study identified important social and environmental risk factors associated with out of hospital deaths during the post-discharge period. We found that factors, such as maternal education, water source, and bed net use, were predictive of out of hospital death. Other home characteristics have been shown to increase the odds of under-five mortality as well, including large family size, poor birth spacing, poor sanitation, and living in a rural environment.[82] Though these aspects may not directly influence child mortality, they likely reflect the socioeconomic status and difficult circumstances within which these families are embedded.

In addition, caregiver attitudes and perceptions were important to health seeking, as they played a significant role in conceptualizing likelihood of recovery and availability of opportunities. When asked what could have saved their child, many caregivers chose to focus on steps that were taken, resources that were accessed, or help that was given, rather than hypothetical areas of improvement. Some wished for access to better health services existing elsewhere, but few focused on potential changes in their immediate environment or health system. With a fatalistic undertone, caregivers often expressed an acceptance of death and the medical resources surrounding them. Perception of the possible or the changeable seemed to be stifled by previous experiences, limited control, and the larger social context.

Studies suggest that limited access to health care in developing countries, resulting from delayed health care seeking or none at all, may be an important determinant of child mortality.[83] Delayed health seeking behavior, observed in our study among others, often stems from poor symptom recognition and caregiver perceptions of health resources.[83–86] Previous studies of acute child illnesses indicate that danger symptoms and disease severity are often not recognized by caregivers.[87,88] A cross-sectional study in Burkina Faso found that clinically defined diarrhea was

recognized by only 55% of caregivers of whom only half then sought care for their child, indicating deficits in the perceived severity of the illness.[89] In addition to perceptions about the illness itself, the perceived etiology, anticipated quality of care, and estimated distance to the health facility influence health seeking behavior, but their relative contributions are less studied.[90]

Caregiver knowledge about health has been shown to protect against child death.[84] Our study, among others, found that maternal education was incrementally correlated with decreased odds of out of hospital death and infection.[91] Maternal education initiatives have been shown effective in decreasing disease incidence and child mortality.[92,93] Regardless of maternal years of schooling, hygiene education interventions have been found to reduce the risk of childhood infections.[94]

Aligning with evidence from the literature, post-discharge interventions should be developed and implemented for children at risk of out of hospital death. An emphasis on developing health knowledge and perceptions of caregivers has the potential to greatly impact child disease and mortality. Given the identified barriers, delayed health seeking could be improved through maternal education on early warning symptoms or through establishment of routine post-discharge care, utilizing the available outpatient heath infrastructure (such as post-discharge follow-up at nearby health centers). In addition to health seeking, promotion of health behaviors within the home environment, such as bed net use and proper hygiene, may improve health outcomes, as these behaviors among others serve as a proxy for overall health knowledge.

Some limitations to the study design should be considered when interpreting results. The sample size was relatively small for quantitative analysis, making the results vulnerable to Type II error. Therefore, only very strong associations were detected. Despite the small sample size, we found several variables with high odds ratios for out of hospital death. Another limitation is the external validity of this study. Our sample was derived from a single region of Uganda and included only discharged patients from two hospitals. The experiences of patients and caregivers from other hospitals and in other countries may be quite different. However, our sampled hospitals included a typical regional government hospital, similar to others in East Africa, and a private mission hospital. This mixture of health facilities provides as diverse a sample as could be derived from a

single area. Further, as this qualitative survey was administered near the end of an ongoing study, differential recall between caregivers whose children recently died compared to those whose children died earlier during the study, may have played a role in the kinds of events which were reported. However, this study used very general questions, and due to the importance of the events, it is unlikely that significant details were forgotten. Finally, this study did not directly ask about facilitators to health care seeking, which is an important aspect for overcoming barriers.

In conclusion, out of hospital death in an important contributor to mortality in children discharged from hospital. Barriers contributing to death outside of hospitals are complex and include financial constraints for transportation, delayed care seeking, and a general unawareness of the risk surrounding the post-discharge period. These occur in the context of poor maternal education and poor health behavior. Interventions aimed at improving both the social context (eg. maternal education) and the health system (eg. emergency transport, post-discharge follow-up) may help to alleviate some of this burden.

Chapter 7. A cohort study of morbidity, mortality and health seeking behavior following rural health center visits by children under 12 in southwestern Uganda

Background

Children who have been discharged from health facilities, especially in developing countries, are at high risk of significant morbidity and mortality. In many instances the short term mortality (weeks to months) associated with hospital discharge may be as high, or higher, than mortality during hospitalization.[56] Despite this increased vulnerability in the post-discharge period, few data exist to characterise the morbidity, mortality and health seeking behavior following primary outpatient, health center visits among rural populations in low income countries. In 2007, Lindblade et al. reported the 30 day mortality rate of 2.4% among 1711 sick children 2-60 months of age presenting to seven rural health facilities in western Kenya during a four month period.[95] Of those who died, 12% died on the same or next day and over 40% died within the first week. However, their admission status following the clinic visit was not reported limiting any conclusions on the morbidity and mortality during the period following out-patient visits. In the full cohort, the most important predictors of death included malnutrition, age less than 24 months, anemia, and severe pneumonia.

Of further importance is that lower level health center visits are a critical component of national health systems in that they not only provide the necessary treatment of acute illness, but that they provide a linkage to larger hospitals for the referral of children who require care beyond their scope. An understanding of the disposition of children following outpatient department visits (and health seeking prior to these visits) is therefore of considerable interest when designing health interventions aimed at improving the care of children following episodes of acute illness.[96] A broad understanding of these issues could assist in the incorporation of simple risk scores to guide admission, referral and outpatient treatment decisions, helping to improve timely intervention among vulnerable children as well as reduce unnecessary intervention. The development of risk scores that can be used at rural health centers by health workers with limited training requires that risk factors, especially clinical risk factors, be measured accurately. Severe pneumonia, consistently identified as an important risk factor for post-discharge mortality, may be useful in such a risk score, but may be difficult to diagnose at rural health centers by health

workers with limited training. We have an interest in using pulse oximetry as a sensitive and repeatable measure of lung injury and its role as indicator of risk while at the same time incorporating other important derived variables such as heart rate.[97] Other variables consistently noted to be associated with post-discharge mortality that should be explored in a post outpatient department (post-OPD) context include nutrition status (weight-for-age z scores) and age.

The purpose of this exploratory study was to identify predictors of both immediate and follow-up morbidity and mortality among children visiting a rural health center in Southwestern Uganda, and to describe in general terms the disposition children following these visits. In addition to exploring associations of variables known to be associated with post-discharge mortality, variables thought to be potentially associated with morbidity and/or mortality following out-patient department visits were also examined.

Methods

Study design

This was a prospective cohort study with recruitment from October2012 to January 2013, with follow-up occurring from November 2012 until May 2013.

Population

The Kyabugimbi Health Center is level IV primary health care centre located in the Bushyenyi District of South Western Uganda at an altitude of approximately 1400 meters. In Uganda, health facilities are divided into health centers and hospitals. Health centers range from level I (lowest – village level) to level IV (highest – county level). Above the level of a health center are three levels of hospital (district, regional, and the national referral hospital). Health centers generally focus on out-patient services although many will have limited in-patient facilities, especially level IV health centers. The Kyabugimbi health center's diagnostic capabilities are limited to those tests able to be easily performed using an optical microscope (blood smear and sputum/stool analysis), or rapid diagnostic tests (urine dipsticks, HIV, malaria). The health center has the capacity to test and refer for HIV treatment (drugs to prevent mother-to-child transmission of HIV are available). This health center can treat the common diseases of childhood including, but not limited to diarrhea, pneumonia, malaria, skin and soft tissue

infections and tuberculosis. This health center conducts health promotion and immunization activities in the community. A referral strategy for these illnesses would be generally based on the national guidelines and IMCI. The catchment population of the Kyabugimbi health center IV is rural and composed primarily of households dependent upon subsistence and small-scale farming or small businesses catering to the immediate needs of the community. The nearest referral center is approximately 25 km away. In this population approximately 17% of children under-five years are considered underweight, 36% stunted and 8% wasted (unpublished data from the baseline survey conducted by Healthy Child Uganda in Bushyenyi District in 2012). The Bushenyi district has recently been the focus of a maternal-child health program, Healthy Child Uganda, funded under the Canadian government's Muskoka Initiative. This has allowed for a substantial investment in the training of volunteer community health workers (village level health center I) and the implementation of the Integrated Community Case Management guidelines.[98] These volunteer community health workers are often the first health workers to assess children who are ill. They are trained to diagnose and treat early stages of malaria, pneumonia and diarrhea in children, as well as identify those children in need of referral to higher levels of care. The drugs available to these community health workers for the treatment of children include oral antibiotics (amoxicillin), oral anti-malarials (artemether-lumefantrine), oral rehydration salts and oral zinc. The Kyabugimbi Health Center IV offers a general service, providing pediatric, adult and maternity care. Limited in-patient pediatric facilities make this health center primarily an outpatient center. Children with more severe disease are referred to higher level health centers. The health center provides care to approximately 10-20 pediatric patients per day, with seasonal fluctuations. Most children accessing care live within 30 minutes of this clinic (either by walking or public transportation). The care is provided primarily by nurses with 1-2 years of training and clinical officers (2-year diploma trained paramedicals with diagnostic and therapeutic training). There are generally no physicians available and the centre operation is primarily during the day time. The Integrated Management of Childhood Illness (IMCI) guidelines form part of the national guidelines of care in the diagnosis and treatment of the most common childhood illnesses and is used at this center.[99]

Eligibility

All children aged 0 – 12 years old presenting with a parent or guardian to the health center between October 10, 2012 and January 31, 2013 between 8am and 5pm on non-holiday weekdays were eligible for enrollment. This time period encompassed both the rainy season and early part of the dry season. Children were only enrolled on one occasion during the course of the study.

Data collection/measurement

Following informed consent, a trained research nurse interviewed the parent/guardian of each child to collect social, demographic, health seeking, health behavior and clinical data. The research nurse obtained and recorded clinical signs including respiratory rate (tapping method)[100], blood pressure (automated), axillary temperature, and using the Phone Oximeter,[62] 1 min photoplethysmogram (PPG), blood oxygen saturation (SpO_2) and heart rate. Anthropomorphic data (height, weight, mid-upper arm circumference) were also measured and recorded. These were recorded separately from the routine examination by the health center staff. The diagnosis made during the visit by health center staff was recorded, as was the outcome of each visit (outpatient treatment, referral, admission, death). All enrolled children received standard care during the sick-child visit. Approximately two to four months following the visit, subjects were visited at their place of residence by a field officer. During the follow-up visit the vital status (alive or dead) as well as all health seeking since the visit were recorded, as recalled by the primary caregiver of the child. The date of each health seeking episode was recorded along with the type of provider seen. PPG recordings were analyzed for artifacts and other quality degradations using Gaussian filters and cross-correlation[101] and sorted according the quality (perfect, acceptable, challenging, last resort, unusable/unavailable) and duration. This automated quality assessment was visually validated by an Anesthesiologist. Median heart rate and SpO2 were extracted from the largest artifact free PPG recording for each subject. Age-dependent demographic variables collected at enrollment were converted to age corrected z-scores according to the World Health Organization Child Growth Standards.[63] 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.[64] The age corrected z-scores for

systolic blood pressure were calculated using subjects' height, according to the procedures previously described.[65]

Outcomes

The primary outcomes were stratified by immediate and follow-up events. Immediate events were those occurring at the time of the initial sick child visit. These were defined (1) admission, (2) death and (3) referral. Admission was defined as an admission to the Kyabugimbi health center IV. Referral was defined as a referral made by the attending clinical officer to a higher level of care. Death was defined by death during the course of admission, or if referred, as death during transport or admission at the referral center.

Follow-up events were those events which occurred within 30 days following the initial health center visit (or following discharge/referral in those who were either admitted or referred) and were exclusive of immediate events. These were defined as a new admission to a health center/hospital, death, or visit to one of five categories of health care providers. The five categories were (1) nurse (2) doctor/clinical officer (3) community health worker (4) traditional healer and (5) untrained health worker. A secondary outcome of death and/or hospital admission within 30 days was also analyzed against potential predictor variables.

Statistical analysis and sample size

Census sampling of all children under 12 years of age attending the clinics during weekday working hours was carried out for 16 weeks. The purpose of this exploratory study was to be hypothesis generating rather than hypothesis testing. We assumed a 10% composite event rate for both immediate and follow-up events. With enrollment of 500 subjects we estimated an accrual of 50 immediate and 50 follow-up events, providing sufficient statistical power to explore possible univariate associations between potential predictor variables and these outcomes. Database preparation was done using R 3.0 (Statistical analysis was conducted in SAS 9.2 (Carey, NC)). Univariate logistic regression was used to model the association between each potential predictor variable and both immediate and follow-up events, with the odds ratio and a 95% CI being the measure of association. Since subjects could be labelled with more than one

diagnosis, the analysis of diagnostic category was done as an adjusted analysis, controlling for all diagnostic categories.

Ethical considerations

This study received research ethics approval from the Mbarara University of Science and Technology, Uganda and the University of British Columbia, Vancouver, Canada. Written informed consent was provided by a parent or guardian of all included subjects.

Results

Over the four-month recruitment period there were 808 sick-child visits, of which 717 were enrolled (89%). Of the 717 enrolled subjects, 604 (84%) received a successful follow-up visit. Of the 91 excluded subjects 78 had no parent/guardian present, 2 were already enrolled, 2 refused consent and the remaining were excluded as their visits were not due to an illness (Figure 7.1). The median age of the children representing the sick child visit was 25 months (IQR 11 – 64) and 360 (50.2%) were male (Table 7.1, Figure 7.2). Most subjects (75.2%) lived within 30 minutes from the health center by public transport and only 3% lived more than 60 minutes from the health center. Over 70% of subjects presented with an illness duration of less than 7 days.

Diagnoses made during the sick child visits were grouped into 10 categories (Table 7.2). Pneumonia, clinical malaria and non-specific respiratory tract infections were the most common infection related diagnoses made, with 23%, 30% and 37% of children receiving these diagnoses, respectively. Sixty percent of subjects had a non-infectious diagnosis (eg. reactive airway disease, trauma, malnutrition etc.), although most of these were diagnosed concurrently with a suspected infection. Six hundred and six of the 717 subjects had a blood smear examined for parasitemia of which 27 (4.5%) were positive. Overall, 651 (91.4%) of children had a suspected infection and 61 (8.6%) were not diagnosed with any infectious illness.

Immediate events

There were 85 (11.9%) immediate events among the 717 sick child visits. Seventy two subjects (10.1%) were admitted following assessment by the clinical officer, 16 (2.2%) were referred to a higher level of care by the clinical officer (three were admitted and referred) and no subjects died

(Table 7.3). An immediate event occurred in 12.1% of children with suspected infections and in 6.6% of children with no suspected infection (risk difference, 5.6%; 95% CI -1.1% to 12.3%).

Among demographic variables distance to health center predicted immediate events, with subjects living between 30 and 60 minutes from the health center having an odds ratio of 1.95 (95% CI 1.15 – 3.31) when compared to those living less than 30 minutes away (Table 7.4). Those living greater than 60 minutes away had a non-significant odds ratio of 2.38 (95% CI 0.77 – 3.46); however only 3.1% of subjects were in this distance category. Neither maternal education, number of siblings nor maternal HIV status was associated with immediate events. Children older than five years had a lower odds of immediate events compared to the reference group of children under 12 months of age (OR 0.45, 95% CI 0.22 – 0.94). Children in the 12 – 24 month category and those in the 24 – 60 month category were not associated with higher odds of immediate events.

Upon analysis of health seeking and behavior variables, having received an antimalarial prior to the visit was highly predictive of an immediate event with an odds ratio of 2.17 (95% CI 1.36 – 3.45). A total of 202 (28%) of subjects had used an antimalarial prior to the sick-child visit. Antimalarial use prior to the health visit was associated with being seen (or referred) by a community health worker ($p<0.0001$) with 60% of those referred by their community health worker having received an antimalarial versus 20% of those not referred. Antibiotic use prior to the sick-child visit occurred in 265 (37%) of subjects, but was not associated with immediate events despite a similar distribution of antibiotics between those referred/seen by their community health worker and those not seen or referred ($p<0.0001$). Having been seen by a community health worker for the presenting illness predicted an immediate outcome (OR 2.03, 95% CI 1.26 – 3.27), while being referred by the community health worker was not associated with this event (OR 1.51, 95% CI 0.88 – 2.57).

Elevated raw and age adjusted respiratory rates and heart rate were associated with immediate events. Elevation in temperature was highly significant, with each degree increase above 36.5 C being associated with an odds ratio of 2.02 (95% CI 1.57 – 2.57) of immediate events. SpO2, analysed as a continuous variable, was associated with an immediate event. For each 1% decrease in SpO2 there was a corresponding 6% increase in the odds of immediate events.

Children who were severely underweight (defined as weight for age z scores less than -3) had a higher odds of immediate events with an odds ratio of 2.72 (95% CI 1.27 – 5.81). Children who were moderately underweight (defined as a weight for age z-score between -2 and -3) did not have a statistically significantly higher odds of immediate events.

An adjusted analysis of the diagnostic categories was made to determine their association with immediate events. Both clinical malaria and pneumonia were highly associated with immediate events with statistically significant odds ratios of 4.50 and 4.13, respectively. Non-specific respiratory tract infections had a strong negative association with immediate events (OR 0.13, 95% CI 0.04 – 0.40).

Follow-up events

Forty-seven (7.8%) events occurred during the first 30 days after the initial sick child visit in the 604 subjects who were successfully followed-up (Table 7.3). During this time 3 (0.5%) children died, 8 (1.3%) were admitted to a higher level of care facility and 44 (7.3%) were taken to one of 5 categories of health care providers. Among the 44 children seen by a health care provider, 19 (44%) were seen by a physician/clinical officer, 10 (23%) by an untrained health worker, eight by a community health worker (18%), 3 (6.8%) by a nurse and none by a traditional healer. The variables associated with early events were not associated with late events. The occurrence of an early event was not associated with follow-up events (OR 1.11, 95% CI 0.45 – 2.71), although few events may have led to type II error. In the demographics and health behavior category the consistent use of a bed nets was paradoxically associated with a higher odds of follow-up events when compared to not using a bed net. In the clinical category only a higher age adjusted z-score for systolic blood pressure was associated with higher odds of the event. A sensitivity analysis of follow-up events in those not experiencing an immediate event was conducted but did not lead to important differences compared to the analysis of the entire cohort (data not shown).

The secondary outcome of admission and/or death within 30 days occurred in 11 study subjects. Analysis of potential predictor variables against this outcome found that a low SpO2, analyzed as a continuous variable, was significantly associated with this event (OR 1.07, 95% CI 1.01 – 1.14) with each percent reduction in SpO2 being associated with an approximate 7% increase in the odds of either death or subsequent admission.

One hundred and thirteen subjects were lost to follow-up (16%). Children who were successfully followed-up were similar to those who were lost to follow-up, although some differences were noted. Statistically significant differences were present in maternal education, number of siblings, baseline respiratory rate and baseline oxygen saturation (Table 7.5).

Discussion

Young age, distance from health facility, previous contact with a community health worker as well as several vital signs were associated with admission or referral following sick-child visits at a rural health center in South Western Uganda, but were not associated with follow-up events including death, subsequent admission or further health seeking behavior. Health centers, rather than hospitals, are often the point of entry for sick children, especially rural children, in sub-Saharan Africa. It is therefore important to understand the epidemiology of sick-child visits in this context. In this exploratory study, children visiting a rural level IV health center for care were enrolled and outcomes were assessed immediately and at one month following their visit.

A recent systematic review of post-discharge morbidity and mortality found that children entering the post-discharge period are vulnerable, often at a higher risk of mortality than during the hospitalization period.[56] While this observation highlights the vulnerability of hospitalized children in resource poor countries, far more children are assessed (primarily as outpatients) at community health centers than at referral centers when ill. These health centers may be far from referral centers and be handicapped by lower staff ratios, less expertise and training, less equipment and less medication. The ability to identify children who remain vulnerable following rural health center visits would be of substantial utility in designing community health interventions which could be applied during health visits. The development of risk-scoring tools that use simple and easily measured variables to predict vulnerability could significantly aid such efforts.

The findings of this study suggest that future studies aiming to link illness related variables to morbidity and mortality following sick-child visits should be designed to capture more clinically significant outcomes, such as death and admission. The frequency of such outcomes (about 2%) in this study partly reflect the difficulty of conducting such studies at the health center level and may be an important reason why so little data currently exist in this area. We estimate that a

study of approximately 5000 subjects would be necessary to accrue the recommended 100 events to be able to reliably attempt the development of a 10-variable prediction tool.[102] While conducting a prospective study to create a clinical prediction model may therefore be more feasible at the hospital level, where the level of illness and risk post-discharge morbidity and mortality are much higher, such a tool may not have sufficient external validity to be applied at the health center level.

Geographic barriers to health care in rural areas have been well described.[103,104] In this study distance was measured by self-reported travel time and self-reported travel costs. In the analysis, transport time but not transport cost, was associated with immediate events. Neither cost nor time was associated with follow-up events. A recent study from rural South Western Uganda found that distance as measured by self-reported time or cost was not associated with missed HIV clinic visits, but that distance as measured by straight-line GPS was highly associated with missed clinic visits.[105] Future studies examining morbidity, mortality and health seeking among pediatric populations should consider using more objective means of distance measurement, such as GPS tracking, rather than self-report.

Prior consultation with a community health worker, but not referral by a community health worker, was associated with immediate events. This suggests that those seen but not referred were more vulnerable than the other enrolled children at the time of the sick child visit compared to those who were referred. No temporal data was collected on the timing of these visits, but it may be the case that those who were not referred were ineffectively treated in the community and therefore had delayed transfer to a higher level of care. Also, those with antimalarial treatment prior to the sick child visit had a higher probability of admission or referral, indicating that perhaps an incorrect malaria diagnosis or inadequate malaria treatment in the community was possible. The fact that most of those who had been either seen or referred by a community health worker had prior exposure to antibiotics or antimalarials suggests that the community health workers commonly provided or recommended the use of these drugs. More research on referral patterns, treatment strategies and outcomes following community health worker visits is required to further understand these observations.

The association between clinical variables and immediate events is not surprising since these variables are closely tied to the decision algorithms used in determining the need for admission and referral. The diagnosis of malaria or pneumonia by the clinic workers was also associated with immediate events, but not follow-up events. This is in contrast to several studies of post hospitalization which clearly show that diagnoses like pneumonia and low weight-for-age Z scores are associated with post-discharge morbidity and mortality.[19,34] Our study, however, was comprised mostly of children who were not admitted and the outcomes of admission and subsequent health-seeking were less robust than outcomes of re-admission and death often used in post-discharge research.

There were too few deaths to conduct any conclusive analyses using this outcome alone. However, a secondary analysis limiting the outcome of interest to death or admission within 30 days (n=11) was not associated with any of the prospectively collected variables with the exception of low SpO2. In this analysis, for each 1% decrease in SpO2 the odds of the negative outcome increased by approximately 7%. The altitude of approximately 1400 meters at the health center resulted in a relatively low median (97.3%) oxygen saturation and would increase the statistical power in identifying children with impaired gas exchange (steep part of the oxygen dissociation curve). Further study on the utility of oxygen saturation as a predictor of post sick child visits is required and this result should be interpreted cautiously since this was a secondary analysis.

This study is subject to several limitations. First, and most importantly, the clinical variables collected for the study during the sick child visit were available for the health care center staff seeing the child. Therefore, although the research nurses did not determine or implement a treatment plan, the additional variables collected may have influenced the decision to admit or refer the subject.

Loss to follow-up was a factor in approximately 16% of enrolled subjects. Those who were lost to follow-up may have been more vulnerable than those who were found and interviewed, limiting our ability to detect important predictors of health seeking following admission. While most characteristics were similar between those found and those lost to follow-up, differences in baseline respiratory rate, oxygen saturation, maternal education and the number of siblings

suggest that those lost to follow-up may have been more vulnerable. The limited sample size and the short period over which this data was collected contributed to both the possibility of type II error as well as limited insight into the seasonal variability of illness and its effect on illness and health seeking following the initial sick child visit. The duration of time between discharge/release from the health center following the sick-child visit and the time of data collection may have led to recall bias. It is possible that mothers were more likely to recall more significant episodes of illness/care seeking and that less significant episodes were missed. Finally, our post-visit outcome combined three different events: death, admission and further health care seeking. Clearly these are very different types of events and it is likely that many instances of health care seeking were for relatively benign conditions and likely to be unrelated to the initial sick child visit. This additional noise in the outcome will significantly limit detection of important parameters present at the visit that are associated with important post-visit illness.

In conclusion, this study showed that sick-child visits at a rural health center in South Western Uganda were associated with rates of mortality and subsequent admission of less than 2% and rates of health seeking of 7% in the 30-day period following the sick child visits. Age, distance to health facility, diagnosis and several clinical variables were associated with immediate events but there were no reliable predictors of 30-day follow-up events identified in this study.

Chapter 8. Pediatric sepsis in Uganda: A prospective cohort study

Background

Pediatric sepsis is defined by the pediatric international consensus conference as the presence of the systemic inflammatory response syndrome (SIRS) in association with a confirmed or suspected infection.[24] The current sepsis definitions consist of a continuum of syndromes progressing from sepsis (above) to severe sepsis to septic shock based on the presence of organ dysfunction. These definitions were initially developed for use in clinical research but have been progressively introduced into clinical care. In adults, for instance, the systemic inflammatory response syndrome, has been incorporated into emergency department early warning for serious infectious illness.[106] These definitions also form the basis for guideline development in both adults and pediatrics in developed countries.[107] In the resource constrained context, however, sepsis as a syndrome is largely absent from the pediatric global health lexicon, with the notable exception of neonatal sepsis. Rather, infectious disease is considered vertically, with a disease specific focus rather than an infectious syndrome based approach.[108] While this approach fits well with the incorporation of disease specific treatment algorithms, it neglects the fact that many diseases exist concurrently, and that a general syndrome of infection may be helpful in defining risk and guiding treatment in these populations.

Although sepsis, with its definitions of increasing severity, may be helpful as early warning signs of risk, only well-resourced centers can actually provide such diagnoses since the resources required are often not available or too costly for routine use. This is a clear and recognized limitation of the current definitions of sepsis.[43] Even the most basic SIRS-based definition of sepsis requires a white blood cell count which is often not available in lower level health facilities. Currently no studies have been conducted in resource constrained settings to determine the prevalence of sepsis, nor its ability to identify children who die of an infectious illness. The purpose of this study is to determine the hospital burden of pediatric sepsis using its most basic definition (SIRS in association with suspected or proven infection) and to evaluate it as an early warning sign of infectious disease associated mortality.

Methods

This study was conducted as a secondary analysis of a previously published study evaluating pediatric post-discharge mortality in Uganda (**Chapters 4 and 5**). The methods have been previously described in detail (**Chapter 4**). Briefly, this was a two-site, hospital-based cohort study in Mbarara, Uganda. This study was approved by the research ethics boards of the University of British Columbia (Vancouver, Canada) and the Mbarara University of Science and Technology (Mbarara, Uganda). Children who were between 6 months and 5 years of age and who were admitted to either site with a suspected or proven infection were eligible for enrollment. Children previously enrolled were excluded. Enrollment occurred between March 2012 and January 2013. A research nurse obtained consent from a parent/guardian of all enrolled children and then collected admission variables including vital signs and blood for a full blood count. Demographic variables including age, sex, known comorbidities, anthropometric variables (weight, length/height, mid-upper arm circumference), length of stay, discharge diagnosis and in-hospital vital status were also obtained. All children received routine care in accordance to the national guidelines during their admission under the care of the hospital medical team.[109] The medical team included pediatricians, medical residents, medical interns, nurses and nursing interns.

Outcomes

The primary outcome was the burden (prevalence) of sepsis (SIRS) among admitted subjects and its performance (sensitivity, specificity and positive/negative predictive values) in predicting death during admission. Sepsis was defined by the pediatric international consensus conference as the presence of the systemic inflammatory response syndrome (SIRS) in association with a confirmed or suspected infection (**Table 8.1**). Since temperature was measured via an axillary probe, it was assumed to be 0.5^{o}C lower than a core temperature. A measured axillary temperature of 38.0^{o}C was therefore assumed to be consistent with a core temperature of 38.5^{o}C.Therefore, the threshold for meeting the hyperthermia cut-off was reduced from 38.5^{o}C to 38.0^{o}C. Secondary outcomes included the proportion of subjects meeting the cut-off points for each component of the sepsis definitions (heart rate, respiratory rate, leukocyte count, temperature) and the proportion of subjects meeting the sepsis definition by each defining

criteria (temperature with leukocyte count, temperature with heart rate, temperature with respiratory rate, leukocyte count with respiratory rate and leukocyte with heart rate) and to determine the predictive performance characteristics of these individual criteria in predicting mortality.

Statistical analysis and sample size

The sample size is 1307 subjects, the sample enrolled for the primary study analysis previously reported (**Chapters 4 and 5**). Analysis was primarily descriptive. Proportions were calculated along with 95% confidence intervals. All analyses were conducted using SAS 9.3 (Carey, NC).

Results

One thousand three hundred and seven (1307) subjects with a confirmed or suspected infection were enrolled following the screening of 1824 subjects during the course of the study (**Figure 8.1**). Of these, 517 (28%) were excluded most often due to not admitted with a confirmed or suspected infectious illness (12% were not enrolled due to consent refusal or since they were already in the study). The most common reasons for exclusion included malnutrition without concurrent infection (n = 192), admission of an already enrolled subject (n = 51), living outside of catchment area (n = 35) and refusal of consent (n = 22). The median age of enrolled subjects was 18 months (IQR 11 – 34) and 717 (54.9%) were male (**Table 8.2**). Among the enrolled subjects, 380 (29.1%) were underweight (weight for age z-score < -2), 473 (36.2%) were wasted (weight for height/length z-score <-2) and 368 (28.5%) were stunted (length/height for age z-score <-2). The most common diagnoses made by the medical team during the course of admission included pneumonia (31%), clinical malaria (50%) and gastroenteritis/diarrhea (8%). The median length of stay was 3 days (IQR 2 – 5).

Sepsis and mortality

Over the course of admission, 65 children died (5.0%). Out of the 1307 subjects enrolled with a confirmed or suspected infection, 1121 (85.9%) met the systemic inflammatory response syndrome criteria, and therefore were defined as having sepsis. Of the 1824 screened subjects, 61% met the sepsis criteria. The sepsis criteria captured 61 out of 64 deaths (1 death was excluded due to missing data resulting in inability to determine SIRS status), demonstrating a

sensitivity and specificity of 95% and 15%, respectively. The corresponding positive and negative predictive values were 5.4% and 98.4%, respectively (**Table 8.3**). Of those who died, 27 (42%), 19 (29%), 7 (11%) and 7 (11%) had a final diagnosis of malaria, pneumonia, diarrhea and meningitis, respectively (**Table 8.4**). Seven (11%) were diagnosed with more than one primary infection (pneumonia + malaria, pneumonia + meningitis etc.) and 8 (12%) were diagnosed with sepsis that was unspecified.

The proportion of children meeting each SIRS criteria and those meeting the sepsis definition based on each combination are shown on **Table 8.3**. Overall, 587 (45%) of subjects had a leukocyte abnormality (12% below the age-threshold and 88% above). One thousand forty two (80%) had a temperature abnormality, of whom 36 (3.5%) were hypothermic and 1006 (96.5%) were hyperthermic. Four hundred and fifty three (35%) had a heart rate abnormality. One thousand two hundred forty six (95%) were tachypneic according the SIRS criteria. For the five combinations of criteria defining SIRS, abnormal temperature with tachypnea was the most sensitive (81%) providing positive and negative predictive values of 4.8% and 93.3%. The combination of abnormal leukocyte with abnormal heart rate was the most specific (84%) in the prediction of mortality (PPV 7.8%; NPV 95.7). The distribution of diagnoses between these groups did not differ substantially.

Three subjects died but were not identified by the SIRS criteria at the time of admission (**Table 8.5**). They died on day 0, day 2 and day 4 of their hospital stay. The child who died on the day of admission was admitted in a comatose state with a Blantyre coma score of 2 (out of 5). While the heart rate, leukocyte count and temperature did not meet the SIRS criteria cut-offs, the respiratory rate was 11 and the oxygen saturation was 62%. The other two study subjects had normal coma scores, and although they had derangements in their vital signs, these were not sufficient to meet the SIRS criteria.

Discussion

This study is the first to quantify the burden of non-neonatal pediatric sepsis, using the international consensus definition, in a typical resource constrained setting in Africa. The burden of sepsis is very high with most children admitted to hospital with a suspected or confirmed infection being septic by this definition. Of all screened subjects (with and without a

proven/suspected infection) over 60% were septic. Further, nearly all enrolled children who died were septic at the time of admission.

Few studies have evaluated SIRS (or SIRS based-sepsis) in the pediatric context. A hospital-wide point-prevalence study from Latvia found that among children with fever, 72% met SIRS criteria.[110] However, given the point-prevalence design, these results cannot be interpreted in the admission phase context. The use of Pediatric Early Warning Scores (PEWS) have been the subject of considerable focus in attempts to develop systems that can effectively risk stratify patients in emergency department setting of developed countries.[111] These PEWS are generally meant to be an adjunct to more established acuity scores such as the Manchester Triage System, Emergency Severity Index or Pediatric Canadian Triage Acuity Score.[112–114]

In resource poor settings, however, triage scores are less well established. The emergency triage assessment and treatment (ETAT) program has been developed and implemented with notable success in Malawi, where significant reductions in in-hospital mortality were observed.[74] This program included the application of a triage system alongside improved coordination with outpatient departments, improved patient flow and extensive training. While triage programs such as ETAT must be encouraged, these could be improved with the integration of simple risk-scoring tools. Another system, the integrated management of childhood illness (IMCI) is well-recognized and increasingly utilized for the diagnosis and treatment of common childhood illnesses in resource poor settings, but has no integrated approach to the triaging of children. The use of danger signs could be used for this purpose, and has been evaluated in Tanzania to determine its predictive characteristics.[115] In this referral hospital in Northern Tanzania, the presence of one more danger signs had a sensitivity and specificity of 76% and 38%, respectively to capture children who died in hospital. In our study, a sole leukocyte abnormality had similar characteristics with a sensitivity and specificity of 72% and 56%, respectively. Our research group's recent analysis of the dataset from which this present study is described has derived a prediction model using only the readily available variables of weight for age z-score, Blantyre coma score and HIV status. Our model had a sensitivity of 83% and specificity of 76% for mortality, significantly higher than either a SIRS based criteria or an IMCI based criteria (**Chapter 9**).

The very high proportion of subjects meeting the sepsis criteria in this study clearly demonstrates the high degree of acuity of children presenting to typical hospitals in East Africa. As a result, further discrimination is necessary above (or instead of) the SIRS based sepsis criteria for any risk-stratification intervention. While defining risk based on the definitions of severe sepsis or septic shock would be an excellent starting point, the resources required for this are not available in the majority of hospitals and health centers in resource poor countries. Of the four criteria used in the SIRS definition, an abnormal respiratory rate, followed by an abnormal temperature, were the most common criteria present at admission, with an abnormal respiratory rate occurring in over 95% of all children admitted with a suspected infectious illness. It is therefore not surprising that the most common combination of criteria fulfilling the sepsis definition is the combined abnormality of temperature and respiratory rate, occurring in more than three quarters of children. The leukocyte count, used alone, appeared to be the most discriminatory variable among the SIRS variables, considering its relatively high sensitivity (72%) along with concurrent high specificity (56%). This confirms the importance of this parameter in the SIRS definition.

Defining sepsis based on the consensus definitions, as in this study, has been demonstrated to capture different children than either more subjective clinical definitions (used by medical teams) or those derived using administrative databases.[116] This underscores the importance working towards a sepsis definition that can be more easily incorporated into clinical research, care and administrative coding. As this work continues, it is imperative that those working in the global health context advocate for the development of definitions suitable for resource poor areas that can be used for both clinical care and for research.

This study is subject to several limitations. First, sepsis criteria were evaluated only at a single point in time, the time of admission. Of the three children who died but did not meet the sepsis definition, only 1 would clearly have likely been septic by the definitions of severe sepsis or septic shock. The others may have fulfilled the sepsis criteria at some later point during their admission, but this was not evaluated. Second, this study only evaluated the presence of SIRS in those with a proven or suspected infection. Of the 517 excluded subjects who were admitted due to non-infectious reasons, the prevalence of SIRS remains unknown in this context. However, the primary objective was to determine the prevalence of sepsis and not SIRS *per se*. Finally, this

study is limited by the fact that it only enrolled subjects from two hospital and therefore may not be representative of other hospitals and health centers in East Africa.

In conclusion, sepsis is present among nearly all children 6 months to 5 years admitted to the hospital in Uganda. The consensus definition of sepsis, while sensitive in capturing children who die during hospitalization, lacks specificity. Other methods of risk stratification should be used to aid in triage in this context and new and more specific definitions of sepsis relevant to this context must be developed.

Chapter 9. Predictors of inpatient-death in two hospitals of Uganda

Background

The fourth United Nations Millennium Development Goal (MDG4) aims to reduce global under five mortality by two thirds from the levels seen in 1990 before the end of 2015.[1] Despite substantial worldwide progress and significant gains in some regions, this achievement will not be reached in most countries of sub Saharan Africa.[3] Currently, over six million children under 5 years of age continue to die annually, of which 3 million occur on the African continent alone.[55] Most of these deaths are due to infectious diseases.[5,55]

Severe infections including pneumonia, malaria and diarrhea remain the most common cause of death in children worldwide. Pneumonia alone kills more than 1.2 million children annually in resource poor countries.[5,8] To help address this burden, the World Health Organization introduced the Integrated Management of Childhood Illness (IMCI) guidelines.[53] These guidelines offer a syndrome based approach to identify major causes of death in children <5 years in resource poor countries. It is generally used in health centers and hospitals and provides standardized treatment protocols for the most common diseases encountered. Whereas the IMCI guidelines provide an approach to the identification and management of common pediatric diseases, they do not provide any risk scores for the identification of children at high risk of mortality. While the IMCI guidelines do provide a list of danger signs for each condition, facilitating an approach for referral decisions, these were not developed for risk scoring per se.

Several risk scoring models have been developed for use in developed countries to determine in-hospital mortality in pediatric patients. The Pediatric Risk of Mortality (PRISM), Pediatric Index of Mortality (PIM) and (PIM2), are models that predict mortality in children admitted to a pediatric intensive care units.[117–119] These models calculate risk based on several physiologic characteristics and can help identify children requiring more focused care.

In resource constrained countries efficient resource utilization is especially important and models that can effectively predict risk could be used to aid in this goal. This may be especially important for children admitted to lower-level health facilities where the capacity to treat critically ill children is absent or limited. In this context, risk scores could play a crucial role in

guiding referral to higher level health centers and hospitals which may be better equipped to care for these children. Models such as PRISM and PIM were derived in developed countries and do not take into consideration major differences seen in children from resource constrained countries, in particular the high prevalence of HIV and malnutrition. Health system limitations for diagnosis, treatment and referral, and social factors such as the prevalence of poor health seeking behavior are also substantially different. Further, the criteria used in the application of these models (base excess, FiO2, time to ventilation etc.) are often not available or relevant in a resource poor context where mechanical ventilation and modern critical care techniques are the exception, not the rule. New models developed in and for a resource poor environment are urgently needed. Where these models have been evaluated in resource poor countries, it has been done in environments atypical to what is generally available in this context. Recently, a risk scoring algorithm for prediction of in-hospital mortality in subjects with respiratory disease has been developed for use in more a typical East African resource poor context.[120] However, this scoring tool is limited to those admitted with respiratory disease and would need to be combined with other predictive tools to be used to evaluate risk in any child with a suspected infectious illness. The emergency triage assessment and treatment (ETAT) program has been developed to improve hospital based care in resource constrained settings.[74] This system has been shown to reduce mortality upon implementation, but could gain from the addition of risk models to improve risk stratification.

The objective of this research is to develop a prediction model of in-hospital death among children admitted with proven or suspected infectious diseases of any etiology. The purpose of this model will be to (1) improve the identification of vulnerable children at hospitals and (2) to be used to aid referral decision-making for children admitted to lower level health centers.

Methods

Population

This two-site study was conducted at the Mbarara Regional Referral Hospital (MRRH) and the Holy Innocents Children's Hospital (HICH), both in Mbarara, Uganda. MRRH is a public hospital funded by the Uganda Ministry of Health and is associated with the Mbarara University of Science and Technology Faculty of Medicine. The pediatrics "Toto" ward admits

approximately 5000 patients per year. HICH is a Catholic children's hospital offering subsidized fee-for-service outpatient and in-patient care in Mbarara and admits approximately 2500 patients annually.

This was a prospective observational study conducted between March 2012 and December 2013 was approved by the institutional review boards at the University of British Columbia (Vancouver, Canada) and the Mbarara University of Science and Technology (Mbarara, Uganda).

Eligibility

Children aged 6-60 months who were admitted for treatment of a proven or suspected infectious illness were eligible for enrollment. Subjects previously enrolled were excluded. Enrollment was continuous and all children meeting inclusion criteria who were admitted during study working hours or within 8 hours of a study shift were considered eligible. Parents or the legal guardians of eligible children were required to provide written informed consent prior to enrollment.

Study procedures

Following enrollment, a research nurse obtained and recorded clinical signs including a 1 minute respiratory rate, blood pressure (automated), axillary temperature, Blantyre coma score, and using a Phone Oximeter, 1 min photoplethysmogram (PPG), blood oxygen saturation (SpO2) and heart rate.(REF) Anthropometric data including height, weight, mid-upper arm circumference was also measured and recorded. Anthropometric data collected at enrollment were converted to weight for age, weight for height and height for age z-scores according to the World Health Organization Child Growth Standards.[63] 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.[64] The age corrected z-scores for systolic blood pressure were calculated using subjects' height, according to the procedures previously described.[65] To incorporate the clinical belief that both excessively high or low temperature reflect deteriorated health conditions, a transformed temperature was used, which was calculated as $17*\log_{10}(37.5\text{-temperature})$ when temperature was less than 37 and as 1.95* temperature -71.3 otherwise. A physiological transformation based on the shape of the relationship between oxygen saturation

and virtual shunt [70*log10(104-SpO2)-57] was used.[121] This virtual shunt was used as an index of disease severity.

A blood sample was taken for measurement of hemoglobin, HIV and a malaria blood smear (microscopy). HIV status was determined using rapid diagnostic test serial algorithm. All positive tests were confirmed by a separate test. Children under 12 months of age with a positive test were confirmed using PCR. Hemoglobin was measured on a Beckman Coulter Ac.T 5diff Cap Pierce 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.

Outcomes

The primary outcome was mortality during the course of hospitalization.

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 selection process (i.e., the optimization to achieve specified sensitivity and specificity cut-offs). One hundred events, corresponding to a total sample of approximately 1000 live-discharges (assuming a mortality rate of 10%, estimated using historical ward data), would be needed to obtain 80% power for ensuring that the lower 95% confidence limit on sensitivity will be at least 75%. An interim analysis of the study showed a mortality rate of approximately 5%. Funding was sufficient to increase enrollment to 1308 subjects.

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.[68] Missing data were imputed using the multiple imputation by chained equations method.[69] Following univariate analysis all variables were included in a multivariable logistic model and the primary model was developed using a stepwise selection process. Variables were removed or added individually minimizing Aikaike's Information Criterion (AIC). AIC was used as a summary measure to compare the overall predictive value across the models. All models which having an AIC value 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 R (Vienna, Austria; http://www.R-project.org).

Results

During the study period, 1824 children met the age criteria (6 months to 5 years) and were screened for eligibility. Of these, 517 (28%) were excluded as they were not admitted with a suspected or proven infectious illness. The most common reasons for exclusion included: malnutrition without concurrent infection (n = 192, 37%), admission of enrolled subject (n = 51, 10%) living outside of catchment area (n = 35, 7%) and refusal of consent (n = 22, 4%), (**Figure 8.1**). 1307 children were consented and enrolled. The median age at admission was 18.2 months (IQR 11.9-33.1) and 717 (54.8%) of subjects were male (**Table 8.1**). The proportion of children severely underweight (weight for age z-score less than -3) was 15.7% and 66 (5.1%) of children were HIV positive. The most common clinician assigned diagnoses included pneumonia (31.4%), clinical malaria (49.7%), and gastroenteritis/diarrhea (7.8%).

Mortality

During the course of admission, 65 (5.0 %) subjects died in the hospital and 1242 (04.9%) were discharged alive. The median time to death was 2 days from admission (IQR 1 – 5). Among those discharged, 120 (9.7%) were discharged against medical advice. Twenty four variables

were tested for their univariate association with mortality (**Table 8.2**). Blantyre Coma Score, dichotomized as normal (score of 5) and abnormal (score of < 5), was highly associated with mortality and provided the highest area under the receiver operating characteristic curve, 0.73(95% CI 0.67 – 0.79) and an abnormal score being associated with an odds ratio of 11.1 (95% CI 6.59 – 18.7). All anthropometric variables were associated with mortality during hospitalization. Low weight for age z-scores (underweight) and weight for height/length z-scores (wasting) provided the best discriminatory power for in hospital death with AUC's of 0.64 (95% CI 0.56 – 0.71 and 0.63 (95% CI 0.55 – 0.70), respectively. Both systolic and diastolic blood pressure were associated with mortality, with raw diastolic pressure providing the highest AUC, 065 (95% CI 0.58 – 0.73). Other clinical variables including temperature, oxygen saturation and HIV diagnosis, oxygen saturation and temperature were also associated with mortality but had lower areas under the ROC curve. Several variables including heart rate, respiratory rate systolic blood pressure, haemoglobin concentration, and parasitemia were not associated with mortality.

Multivariate prediction model

Three models were developed for prediction of mortality. A primary model was developed using any of the available variables. Subsequent models were derived which selectively excluded certain variables from the primary model to ensure that prediction could be possible in the absence of certain variables which may not be available at all centers.

The first model included weight for age z-score, Blantyre coma score and HIV status. The model equation was: logit [Pr (In-patient mortality)] $-1.78 + (-0.26$; weight for age z-score) -2.50 (normal Blantyre coma score) $+1.32$ (Positive HIV diagnosis) and the area under the receiver operator characteristic curve was 0.85 (95%CI 0.80-0.89). At a probability cut-off of 0.030, this model had a sensitivity of 0.83 (95% CI 0.0.74-0.92) and a specificity of 0.76 (95% CI 0.73 – 0.78). We would expect the positive predictive value to be 0.15 (95% CI 0.11 – 0.19) and the negative predictive value to be 0.99 (95% CI 0.98 – 1.00) (**Table 8.3**, **Table 8.4**, **Figure 8.2**).

Model 2 replaced weight for age z-score in model 1 with mid-upper arm circumference, a variable that is more easily obtainable, especially in poorly resourced areas. The model equation was: logit[Pr(In-patient mortality)]$2.02 + (-0.02$; muac in mm$) - 2.54$ (normal Blantyre coma score)$+1.33$ (Positive HIV diagnosis). The area under the ROC curve was 0.84 (95% CI 0.79-

0.89). At a probability cut-off of 0.030 this model had a sensitivity of 0.80 (95% CI 0.70 – 0.90) and specificity of 0.76 (95% CI 0.74 – 0.79) and we would expect the positive predictive value and negative predictive value of 0.15 (95% CI 0.11 – 0.19) and 0.99 (95% CI 0.98 – 1.00), respectively, in a population similar to the derivation cohort (**Table 8.3**, **Table 8.4**).

Model 3 included MUAC and Blantyre coma score and excluded HIV. The model equation was: logit[Pr(In-patient mortality)]$2.77 + (-0.03$; muac in mm$) - 2.47$ (normal Blantyre coma score). The area under the ROC curve for this model was 0.82 (95% CI 0.77-0.87). At a probability cut-off of 0.30 this model had a sensitivity of 0.82 (95% CI 0.72 – 0.91) and a specificity of 0.71 (95% CI 0.68 – 0.73). The expected positive and negative predictive values would be 0.13 (95% CI 010 – 0.16) and 0.99 (0.98 – 0.99) (**Table 8.3**, **Table 8.4**).

Discussion

This study represents a systematic approach to creating an in-hospital mortality prediction tool for the under 5 pediatric population admitted with an infectious illness in a resource poor environment. The model developed is parsimonious, using only age, weight, Blantyre coma score and HIV status to determine the probability of in-hospital mortality. Variables used in the development of the prediction model included only those thought to be both easily and reliably obtainable in most resource constrained contexts. Alternate models were developed incorporating different elements to ensure prediction would be possible in situations where certain variables may not be available.

In the context of limited resources, rapid risk determination is of critical importance. The implementation of an improved triage and training system (ETAT) alongside improvements in patient flow was shown to decrease in-patient mortality, especially early in-patient mortality.(Molyneux WHO Bull 2006) Prediction models such as the one derived in this study could be used alongside a comprehensive strategy such as ETAT to improve care at the point of admission and focus human (eg. nursing) and clinical (eg. oxygen) resources on those children at highest risk of mortality. The determination of risk could play a unique role in sub-Saharan Africa where critically ill children admitted to lower level health centers require sufficient time to travel to referral hospitals. Further, as referral decisions are often made by non-physician health care providers, decision tools such as these could offer substantial aid with minimal

training to ensure that those at high risk of mortality are referred. Using a risk-cut-off of 0.30, the referral population would have a mortality risk of 15% (95% CI 11% - 19%) compared to a mortality risk of 1% (95% CI 0% - 2%) in those not referred, if similar to the admitted sample in this study.

Other models developed for mortality prediction in settings without resource constraints have been evaluated in resource constrained settings have been shown to not perform adequately. A critical difference in the populations in whom models such as PRISM were derived is the much lower prevalence of moderate and severe malnutrition. In this present study an anthropometric measure played a crucial role in all derived models, providing a majority of the discriminatory power in final model. Malnutrition as an independent and critical contributor to infectious disease morbidity and mortality cannot be over emphasized and should be considered as an important component of the evaluation of any infectious illness. In addition to malnutrition, an abnormal Blantyre coma score was also of critical importance, proving more discriminatory than vital signs in predicting mortality.

Although the Integrated Management of Childhood Illness algorithm was not designed as a prediction tool, it does provide referral criteria, listed as danger signs. A recent study from Tanzania evaluated the predictive utility of these criteria for in-hospital mortality. Among 387 children aged 2 months to 5 years, and an overall mortality rate of 7.4%, one or more IMCI danger sign had a sensitivity of 72% (95% CI 56% - 88%) for predicting in-hospital death and would identify 38% of subjects as high-risk.[115] Using a cut-off of 0.30, our model, using fewer and more reliably obtained variables, has a higher sensitivity of 0.83 (95% CI 0.74 – 0.92) and would only identify approximately 25% as high-risk, allowing for a more efficient utilization of resources.

This study was limited by fewer cases of the primary outcome (in-hospital mortality) than was initially anticipated. Although designed to derive prediction models using 100 outcomes, this enrolled only 65 children who died in-hospital. Despite the relatively low number of outcomes our primary model had an AUC of the receiver operating characteristic curve of 0.85 with the lower limit being 0.80, highlighting the excellent discriminating ability of the final model and the utility of each of the predictive variables in the model. A further limitation is the lack of external

validity. Although a major strength of this study was its development using more than 1 hospital, these results require confirmation at other hospitals in other resource poor countries for further calibration prior to recommending their uptake. This is of particular importance if used to aid in referral decision making at lower level health centers, as admission criteria are certainly different than in larger hospitals producing a unique population of children.

In conclusion, a parsimonious prediction tool using easily collected predictors can be used to efficiently predict in-hospital mortality. Further research to externally validate this model is required prior to widespread implementation.

Chapter 10. Conclusion

The burden of post-discharge mortality following serious infection in Uganda is significant and is likely a reflection of the situation in most of sub-Saharan Africa and many parts of Asia. While this dissertation focused primarily on the burden of post-discharge mortality and its prediction, this cannot be examined in isolation. The broader context of this problem is the burden of acute serious infectious diseases (i.e. sepsis) in resource poor countries, the most common cause of mortality in children.[55] Addressing issues related to sepsis requires a comprehensive strategy encompassing prevention, early identification and transport to health facilities, effective triage and treatment in hospital and, finally, post-discharge care throughout the vulnerable period following discharge. Areas of intervention, therefore, must focus on these different components.

Primary conclusions

Basic epidemiology of post-discharge mortality

The current state of knowledge of post-discharge mortality in resource poor countries to date has been limited. The published systematic review of available literature on this topic, presented in Chapter 2, was an important first step in improving the understanding of the important risk factors for mortality after discharge, the limitations of research to date, as well as to provide a general overview of the current state of knowledge on this important issue. This analysis clearly makes a case to improve and increase research on post-discharge mortality and identifies the key research gaps. These included (1) the need for high quality prospective research and (2) the need for prediction for the ultimate purpose of developing post-discharge interventions.

Utilizing the result of the systematic review, a large cohort study of post-discharge mortality was designed. With an understanding of the broader context of sepsis, this study was designed to answer several important and related questions. First, it was designed to improve our understanding of the basic epidemiology of post-discharge mortality. Second, it was designed for the purpose of developing a post-discharge prediction tool. Major secondary objectives also included the design of an in-hospital mortality risk stratification tool as well as a means to determine the burden of syndromic sepsis among admitted children.

While the epidemiology of post-discharge mortality has been examined in several previously published research investigations[19,20,23], all prior studies were either overly broad or too focused, as emphasized in the systematic review. In those studies, which capture a broad population, they included children with and without infectious disease. Admissions related to trauma, cancer, and various chronic diseases are categorically different than those admitted with an acute infectious disease. As a result, the degrees of vulnerability among these children, and the factors associated with this vulnerability, are likely to be very different. Those populations that were highly selected included children with similar disease etiologies such as pneumonia, diarrhea or malaria. These diseases are often based on poorly defined criteria, limiting their external application. Further, these diseases are complicated by frequent overlap with other infections (such as malaria and pneumonia). Finally, when considering the broader context of sepsis, it can be understood that all infectious diseases, when left untreated, follow a common pathway of inflammation with progressive organ dysfunction.

While the results of our cohort study largely confirmed previous epidemiological observations, several new and important observations were identified. First, re-admission data following discharge were generally not collected in previous studies, and when they were, no statistical modelling was conducted to determine if any factors were associated with this outcome. This study found that re-admission following discharge was high, occurring in approximately 17% of individuals. We found that several risk factors including severe malnutrition (mid-upper arm circumference less than 115mm), previous hospitalizations, low oxygen saturation at admission and a diagnosis of pneumonia during hospitalization were all important risk factors for the composite of death or re-admission. Second, this cohort study also observed the high proportion of post-discharge deaths occurring outside of a hospital context. In this study, only 33% of post-discharge deaths occurred during a re-admission. This finding led to the design of a primarily qualitative follow-up study (Chapter 6) to evaluate some of the narratives as expressed by the caregivers of children who died outside of a hospital.

Prediction of mortality in-hospital and following discharge

A further objective of our cohort study was to derive prediction models for relevant outcomes. The most relevant of these outcomes was, and remains, post-discharge mortality. Although this

event occurs as often as in-hospital mortality, no guideline currently exists to address this burden. That these deaths often go unrecognized further distances the health systems in resource poor countries from understanding and acknowledging this problem. Further, even when recognized, the scarcity of resources in the areas most affected constrains the introduction of meaningful interventions if it were to be applied to all discharged children. The development of easily applied prediction tools could quickly identify and stratify those children in need in need of more or less intensive interventions, thus utilizing limited resources with increased efficiency.

Among the most important aspects of designing a study for the derivation of a prediction model is the selection of candidate predictor variables. Obstacles in the selection of candidate variables include not only their potential ability to predict mortality, but also their typical availability in a resource constrained setting, their costs and the time required to collect them. Since these important obstacles could not reliably be overcome using only the expertise of the study team, a modified Delphi process was undertaken to ensure that an optimal list of candidate predictor variables was selected to be included in the main cohort study. As reported in Chapter 3, this process utilized experts in all relevant areas of research and practice. From the initial list of 17 potential predictor variables, derived using previous research and the expertise of our investigative team, 8 were removed with the final list including 30 potential predictor variables based on the recommendations of the participants. This process ensured that the final list of variables to be included in the main cohort study was both sensitive in including the most important candidate predictor variables and specific in ensuring unwanted variables would be identified as such and excluded.

The derivation of a prediction model for post-discharge mortality was explored in Chapter 4 and is an important contribution to pediatric global health. Using only four to six variables that can be easily, reliably and economically collected at admission, children can be stratified into high and low risk categories with sensitivity of over 80% and specificity of over 60% (positive and negative predictive values of about 10% and 98.5%, respectively). The implementation of such a model into routine care would improve the efficiency of subsequently developed discharge interventions. Such models allow for focused interventions that are limited to only high risk individuals or multi-level interventions with increased intervention intensity based on the level of risk. While further work is required in (1) externally validating these data and (2) expanding

these models to both younger and older children, this is a critical first step towards improving post-discharge care in children.

The prediction of in-hospital mortality was an important secondary objective of the main cohort study. Currently, little is available to determine in-hospital risk among children admitted in resource poor countries. Risk scoring models that have been derived in developed countries have been evaluated in resource poor setting and been shown not to perform well. Further, many scoring systems derived in developed countries require variables often not available in the resource poor context. An important potential application of an in-hospital mortality prediction tool is its use in subjects admitted in lower level health facilities. In these facilities, the timely referral of critically ill children to higher levels of care (with resources such as oxygen and physicians) is likely to play a major role in survival. The models derived in this study (Chapter 7) achieved high levels of sensitivity and specificity (approximately 80% and 75%, respectively) with positive and negative predictive values of 15% and 99%, respectively. An important limitation is that these models were derived in higher level health centers rather than lower level health centers, where referrals would actually occur. Nevertheless, this is an important first step for such a validation study.

Out of hospital mortality after discharge

An interim analysis of the primary cohort study indicated that post-discharge deaths were often not occurring during re-admissions. In light of this, and previously reported studies of out-of-hospital mortality in children with acute infectious illness[7,20] we designed a qualitative study of all children who died following discharge but were not re-admitted. This study captured some of the narrative, as expressed by the primary caregivers, of the events surrounding the death of their child. This narrative was focused around 8 questions and is the first study of this topic conducted in a resource poor setting. Results of the qualitative interviews identified several key barriers experienced by caregivers that could be addressed in interventions aimed at improving post-discharge care. Among the possible areas of intervention that were identified in this study, four key areas emerged and include (1) risk awareness (2) early identification of recurrent illness (3) improved health behavior (such as consistent bed net use) and (4) timely health seeking. These

areas have been woven into a recently funded phase I study of a post-discharge intervention which we are currently conducting in Mbarara, Uganda.

Burden of sepsis

A final objective of the primary cohort study was to establish the importance of the burden of sepsis in the resource poor context (Chapter 8). With eligibility focused on children with proven or suspected infections, this secondary objective was readily obtainable. Our results indicated that most (>85%) infectious disease related admissions were associated with a sepsis diagnosis (consensus definition). This is the first study to identify the burden of sepsis among admitted children in a resource poor setting and thus fills an important gap in current research. These results are likely representative of much of sub-Saharan Africa and provide the necessary evidence that the burden of sepsis in resource poor setting is substantial. While the burden of sepsis is high, the current definition of sepsis is very non-specific and does not adequately select a group of children that are particularly vulnerable during their hospital course. Since admission in the resource constrained context already selects a population of children with a much higher mortality risk compared to admissions in developing countries, the use of the SIRS-based sepsis criteria are therefore not likely to be of much utility in this context. A much more useful risk-scoring tool was described earlier (Chapter 7) which can more fully differentiate those at high and low risk of in-hospital mortality following admission.

Health seeking following outpatient department visits

While it is clear that the burden of mortality following hospital admissions is high, little is known about the vulnerability of children following outpatient department visits. It is essential that risk assessment occur not only in children admitted to hospital but also to those seen in the community setting. While our cohort study clearly established the need for improved health care utilization following discharge, it has long been recognized that decisions surrounding the diagnosis and treatment of children within the community setting is vitally important. As an initial step towards gaining further insight into the morbidity, mortality and health seeking following out-patient department visits, we designed and conducted a phase I preliminary study of these events at a rural health center in the community of Kyabugimbi, Uganda. Our finding suggested that while admission and referral decisions are strongly associated with clinical signs

and symptoms in the presenting child, these clinical signs and symptoms are not associated with health seeking following these visits. The reasons for this are unclear, but it may be the case that factors such as educational attainment, and good health practices (such as bed net use) may be more important factors associated with health seeking behavior than the degree of illness. This was the case in our previous study of the health seeking among children who died after discharge (Chapter 6). The evaluation of factors associated with post out-patient department mortality may be a more important association, which requires a much larger study.

Application and future directions

Our work in Uganda has led to several key findings that require further exploration. Three key areas of further research include (1) gaining a more granular understanding of causes of post-discharge mortality (2) the transformation of prediction models into usable applications and (3), the development and evaluation of interventions, primarily in the area of discharge and post-discharge care, that can be applied to vulnerable subjects based upon their level of risk. Finally, once suitable interventions have been developed, these must be adopted and scaled within the health system. Within these health systems, surveillance is essential in the measurement of impact and the ongoing evaluation of the adopted interventions at the population level. A preliminary program of investigation, funded by a Grand Challenges Canada Rising Stars in Global Health, is currently underway in Mbarara, Uganda and is beginning to further some of the work in this area. This program of research is built upon our previous work and is a reflection of its importance and its importance in improving child-health in the resource poor context.

<u>Causal research in post-discharge morbidity and mortality</u>

Currently, little is known about the etiology of post-discharge mortality and whether the causes of the index admission reflect the causes of mortality. Research incorporating the use of verbal autopsies could further our understanding in this area. Knowledge of diagnoses during the post-discharge period would also inform the development of discharge interventions. Further work on how quality of care during admission, or premature discharge, reflects mortality after discharge is also required. Iterative improvements in care throughout resource poor regions will undoubtedly result in a modification of the effect of established predictors of post-discharge

mortality, as will the incorporation of routine discharge interventions, therefore ongoing work on risk prediction will be required.

Usable application of prediction models

Prediction models are mathematically complex and require either simplification or integration with software capable of performing these tasks. The use of mobile phones in sub-Saharan Africa is common and their integration into mobile health initiatives is increasing. We are developing a mobile phone based application incorporating our previously developed prediction models. In-depth testing of our prototype mobile application will be conducted in Uganda using robust mixed-methods techniques including a think-a-loud process[122] and a modified Computer System Usability Questionnaire (CSUQ).[123]

The integration of our prediction models into a usable mobile application will allow for rapid identification of children at the time of admission who are at high risk of mortality during, but especially following, discharge. Using this tool clinicians will be able to ensure that caregivers of vulnerable children receive appropriate care and counselling at the time of discharge.

Discharge interventions

The creation of a prediction models assumes their eventual application to identify vulnerable children requiring intervention. We are currently evaluating the usability and acceptability of a post-discharge bundle (discharge kit + referral) among children discharged in Mbarara, Uganda.

Discharge kit

Post-discharge vulnerability is currently a neglected issue in resource constrained settings. This neglect is due almost entirely to a lack of awareness, by both health workers and families, of the risk children experience during this period. A critical step in beginning to address this issue is to ensure caregivers are aware of the risks their children will face during this period and have an appropriate response any deterioration in health that their child may experience.

To address this need our group has developed a discharge kit for evaluation, its purpose to ensure that caregivers are sufficiently equipped to enter the post-discharge period with their child. The discharge kit is primarily an educational intervention which must be facilitated by a nurse or

other trained health worker. In addition to the educational component, it also contains an insecticide treated bed net, oral rehydration salts and soap as an educational incentive and behavior facilitator. The discharge kit is being evaluated in a post-discharge context and will focus on retention of educational materials presented in the discharge kit and elicit overall satisfaction with the different educational components of the discharge kit.

Back-referral program

The model for health referrals in Uganda, and elsewhere in sub-Saharan Africa, is primarily unidirectional from lower level health centers to higher level health centers. Children who are too ill to be treated at lower level health centers are referred to a center with improved capacity for diagnosis and treatment. Children who are vulnerable during the post-discharge period should be evaluated by trained health workers to ensure that the child's recovery is progressing. A back-referral to lower level health centers addresses this problem directly and engages health workers at lower level facilities to participate in the care of children during the critical weeks and months after discharge. We are currently engaged in the evaluation of the success and acceptability of such a back-referral program in Mbarara, Uganda.

Health system integration

The development of any intervention must consider the health system into which it will be applied. For interventions to be adopted, it is not only important to understand the needs of the health system, as identified through preliminary research, but also for these needs to be clearly recognized by policy makers, health workers, and ultimately the users of the health system. Knowledge translation focused towards these three key areas must form a significant aspect of this process. Collaboration between academia, hospitals, non-governmental organizations and policy makers must also be established early.

Some relevant health system considerations applicable to post-discharge interventions include understanding the linkages that exist (or do not exist) between the various levels of health centers and hospitals and the barriers of accessing care (such as transportation), transitioning care (referrals) and completing care (transportation, follow-up etc.). A corruption of these linkages is an important contributor to the survival of children who have entered the health system.[96] A deep

understanding of these issues in regions of interest will help to guide the process of integrating post-discharge interventions for the ultimate strengthening of these health systems.

Surveillance systems to reduce post-discharge mortality

For the economic and health impact of post-discharge interventions to be measured, there must exist a system which captures the key indicators necessary for such assessments. Vital statistics are among those indicators which would be required to be able to adequately assess any such intervention within a population. Significant progress seen in developed nations in the early 20th century can be, at least in part, credited to being able to measure progress as scale. Currently, the only country in sub-Saharan Africa measuring more than 50% of deaths in a vital registration system is South Africa.[124] In the absence of national surveillance, regional surveillance would significantly assist in efforts to measure the impact of post-discharge interventions. The use of community health workers has been explored as a means to conduct such surveillance.[125]

Conclusions

During this research program, we have established the burden and predictability of post-discharge mortality among children 6 months to 5 years of age in Mbarara, Uganda. We have also furthered the understanding of caregiver context in pediatric post-discharge mortality, a critical component for the development of discharge interventions. We have also established several secondary but important research questions relating to the general subject area of sepsis. This has included development of prediction models for in-hospital mortality in children with infections and furthering the understanding of the burden of sepsis and its role in hospital mortality related to infectious diseases. This work is leading to further research and intervention with potential to have significant impact on overall child mortality.

Tables

Table 1.1a. Systemic inflammatory response syndrome (SIRS)

Presence of ***at least 2*** of the following one of which must be abnormal temperature or leukocyte count

- Core temperature >38.5ºC or <36ºC
- Tachycardia or Bradycardia (see below) in the absence of external stimulus, drugs etc.
- Tachypnea (see below) not related to underlying neuromuscular disease or anasthesia
- Leukocyte count elevated or depressed (see below)

Infection

- Suspected or proven infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection

Table 1.1b. Age specific vital sign cut-offs for SIRS definition

Age group	Heart Rate, Beats/Min		Respiratory Rate, Breaths/Min	Leukocyte Count x $10^3/mm^3$
	Tachycardia	Bradycardia		
1 mo – 1 yr	> 180	< 90	> 34	> 17.5 or < 5
2 yr – 5 yr	> 140	N/A	> 22	> 15.5 or < 6

Table 2.1. Characteristics of studies included in systematic review

Ref.	Design	Dates	Country	Age	Population	Locale	N	FU Proportion	FU Method	FU Times	IP death	PD death	PD death in hospital	PD re-admit	Obs. Period
Studies of all pediatric hospital admissions															
[20]	Retrospective Cohort	1991-1996	Guinea-Bissau	(81%< 5y)	All Admits	NR	3373	NA	Surveillance	NA	12.1%	6.10%	23.1%	11.6%	12m
[19]	Retrospective Cohort	2003-2008	Kenya	0-15y	All Admits	Mixed	14971	NA	Surveillance	NA	NR	4.50%	NR	NR	12m
[17]	Prospective Cohort	1991	Kenya	0-5y	All Admits	Mixed	1223	96%	CV & HV	4, 8w	10%	13%	NR	NR	8w
Studies of admissions secondary to anemia															
[23]	CC with longitudinal FU	2002-2004	Malawi	6-60m	Anemia (Hg<50g/L)	Mixed	377	82.20%	CV	1, 3, 6, 12,18m	6.4%	11.6%	"most"	17.2%	18m
				7-60m	Any other condition	Mixed	373	80.40%	CV	1, 3, 6, 12,18m	0.0%	2.7%	"most"	9.4%	18m
Studies of admissions secondary to malaria															
[33]	RCT	2006-2009	Malawi	4-59m	IPTpd	Mixed	706	95%	PCD	1, 2, 3, 6m	NA	2.6%	NR	19%	6m
				5-59m	Placebo	Mixed	708	95%	PCD	1, 2, 3, 6m	NA	2.4%	NR	19%	7m
[22]	RCT	2004-2006	Guinea-Bissau	3-60m	Severe malaria	NR	951	95%	CV & HV	28d after admission	7.2%	2.0%	NR	NR	28d post admit
Studies of admissions secondary to diarrhea															
[49]	Prospective cohort	1979	Bangladesh	3m-3y	Diarrhea	Rural	551	NR	NR	NR	NA	4.2%	NR	NR	12m
[46]	Prospective cohort	1991-1992	Bangladesh	1-23m	Diarrhea	Urban	500	85% at 6w, 80% at 12w	HV	6, 12w	NA	7%	53%	NR	12w
[48]	Retrospective cohort	1983-1983	Bangladesh	24-72m	Diarrhea	Urban	74	93%	HV	Approx. 4m	NR	2.9%	NR	NR	Approx. 4m

Locale: Urban, rural or mixed; NA: Not applicable; NR: Not Reported; FU: Follow-up; PD: Post-discharge: IP: In-patient; CV: Clinic Visit; HV Home Visit; IPTpd: Intermitted preventative therapy post-discharge; PCD: Passive case detection; LRTI: Lower respiratory tract infection; DRC: Democratic Republic of Congo; PEM: Protein Energy Malnutrition

Table 2.1. Continued

Ref.	Design	Dates	Country	Age	Population	Locale	N	FU proportion	FU method	FU times	IP death	PD death	PD death in hospital	PD re-admit	Obs. period
Studies of admissions secondary to pneumonia															
[21]	RCT	1993-1997	Tanzania	6-60m	Pneumonia	NR	687	89%	CV	Monthly	3%	10%	NR	NR	24m
[42]	RCT	2006-2008	Bangladesh	2-59m	Severe pneumonia	Urban	180	90%	CV	Every 2w	0%	1%	NR	6%	3m
[34]	CC with longitudinal FU	1992-1997	The Gambia	0-5m	LRTI, SpO2 <90	Mixed	83	64%	CV & HV	Once	NR	15%	NR	NR	mean 41m
					LRTI, SpO2 ≥90	Mixed	107	61%	CV & HV	Once	NR	6%	NR	NR	mean 34m
Studies of admissions secondary to malnutrition															
[47]	Prospective cohort	1970	DRC	NR	PEM	NR	171	76	CV	Annually	NA	18%	NR	NR	5y

Locale: Urban, rural or mixed; NA: Not applicable; NR: Not Reported; FU: Follow-up; PD: Post-discharge: IP: In-patient; CV: Clinic Visit; HV Home Visit; IPTpd: Intermitted preventative therapy post-discharge; PCD: Passive case detection; LRTI: Lower respiratory tract infection; DRC: Democratic Republic of Congo; PEM: Protein Energy Malnutrition

Table 2.2. Timing of post-discharge deaths

Study	Population	Obs. period	Time-point for 50% of PD deaths	Other mortality statistic
[46]	1-23m with diarrhea	12w	10d	
[49]	3m-3y with diarrhea	12m	30d	
[20]	All pediatric admissions	12m	60d	
[17]	0-5y all admissions	8w		82% PD deaths at 4w
[21]	6-60m with pneumonia	24m		80% PD deaths at 12m
[47]	malnutrition	5y		>50% PD deaths at 1y
[23]	6-60m with anemia	18m		71% at PD deaths at 6m*

* Cases

Table 2.3. Risk factors for post-discharge mortality

Ref.	Population	Risk factors for post-discharge mortality	Adjusted RR or HR (95% CI)
Studies of all pediatric admissions			
[19]	All admissions	Age 1-5m	1.34 (0.93-1.92)
		Age 6-11m	0.82 (0.57-1.18)
		Age 2-5y	0.57 (0.36-0.90)
		Weight-for-age Z score < -3	3.42 (2.5-4.68)
		Weight-for-age Z score < -4	6.53 (4.85-8.80)
		Parasitemia	0.45 (0.29-0.71)
		Hypoxia	2.30 (1.64-3.23)
		Bacteremia	1.77 (1.15-2.74)
		Jaundice	1.77 (1.08-2.91)
		Hepatomegaly	2.34 (1.60-3.42)
		Hospitalization > 13d	1.83 (1.33)
		1 prior discharge	2.83 (2.04)
		2 prior discharges	7.06 (4.09-12.21)
		≥3 prior discharges	23.55 (10.70-51.84)
		Mild pneumonia	2.30 (1.00-5.28)
		Severe pneumonia	1.37 (1.05-1.79)
		Very severe pneumonia	4.09 (2.25-7.46)
		Severe malnutrition	4.37 (2.73-7.01)
		Meningitis	2.29 (1.57-3.32)
		Sick young infant	2.67 (1.98-3.58)
		HIV	2.22 p=0.19
		Absconded	2.06 p=0.95
[20]	All admissions	Mother educated	0.74 (0.55-0.99)
		Discharged against medical advice	8.51 (5.32-13.59)
		Anemia (vs. malaria)	1.97 (1.07-3.63)
		Diarrhea (vs. malaria)	1.82 (1.21-2.74)
		Pneumonia (vs. malaria)	0.98 (0.65-1.51)
		Measles (vs. malaria)	0.77 (0.36-1.64)
		≥5y (vs. 1-12m)	0.15 (0.07-0.30)
		4-5y (vs. 1-12m)	0.23 (0.10-0.59)
		3-4y (vs. 1-12m)	0.14 (0.06-0.35)
		2-3y (vs. 1-12m)	0.52 (0.33-0.81)
		1-2y (vs. 1-12m)	0.82 (0.59-1.13)
		Neonatal (vs. 1-12m)	0.69 (0.31-1.55)

Table 2.3. Continued.

Ref.	Population	Risk factors for post-discharge mortality	Adjusted RR or HR (95% CI)
Studies of anemia admissions			
[23]	Anemia (Hg<50g/L) admissions	Increase in age (months)	0.92 (0.87-0.97)
		Rural (vs. urban)	1.63 (0.63-3.52)
		Male (vs. female)	1.54 (0.68-3.52)
		Parental unemployment	4.15 (1.61-10.74)
		Splenomegaly	0.36 (0.16-0.80)
		HIV	10.49 (4.05-27.20)
		Bacteremia	2.17 (0.84-5.64)
Studies of diarrhea admissions			
[46]	Diarrhea admissions	Age (1-6m vs. 6-24m)	4.57 (2.90-7.18)
		Sex (Female)	1.73 (1.14-2.65)
		Maternal Education (none vs. ≥ 1y)	2.12 (1.37-3.28)
		Child was not breastfed	2.35 (1.44-3.84)
		Weight-for-age median <60% vs. ≥ 60%	1.04 (0.57-1.89)
		Length-for-age median <85% vs. ≥ 85%	2.97 (1.43-6.16)
Studies of pneumonia admissions			
[34]	Pneumonia admissions	Weight-for-age Z-Score < -2	3.2 (1.03-10.29)
		Length of stay	SS* (RR not reported)

* Statistically significant

Table 3.1. Initial list of candidate predictor variables, N=17

Clinical	**Laboratory**	**Social/Demographic**
Vital signs (HR, RR, BP, T)	Hemoglobin	Age
Oxygen saturation	Blood Culture	Sex
Height	Zinc Level	Maternal Education
Weight		Wealth
Hib, Pneumococcal vaccination		Distance from health facility
Length of stay		
Co-morbidities		
Admission diagnosis		
Discharge AMA		

HR = heart rate, RR = respiratory rate, BP = blood pressure, T = temperature, Hib = haemophilus influenzae type b, AMA = against medical advice

Table 3.2. Applicability of proposed candidate predictor variables as predictors: Stage 1

Candidate predictor	Responses Total N = 23	Applicability, n (%) High	Moderate	Unlikely	Not at all
Clinical variables					
Vital Signs	19	14 (74%)	4 (21%)	1 (5%)	0
Oxygen Saturation	18	16 (89%)	2 (11%)	0	0
Height and weight	19	16 (84%)	1 (5%)	2 (11%)	0
Vaccine history	19	13 (68%)	6 (32%)	0	0
Antibiotic history	19	9 (47%)	8 (42%)	2 (11%)	0
Length of stay	18	11 (61%)	7 (39%)	0	0
Co-morbidities	19	17 (90%)	2 (11%)		0
Admit diagnosis	19	15 (79%)	3 (16%)	1 (5%)	0
Discharge AMA	18	11 (61%)	4 (22%)	2 (11%)	1 (5%)
Laboratory variables					
Hemoglobin level	17	8 (47%)	8 (47%)	1 (6%)	0
Blood culture	18	12 (67%)	6 (33%)	0	0
Zinc level	14	4 (29%)	7 (50%)	2 (14%)	1 (7%)
Social and demographic variables					
Age	17	16 (94%)	1 (6%)	0	0
Sex	17	9 (53%)	4 (24%)	3 (18%)	1 (6%)
Maternal education	17	14 (82%)	2 (12%)	1 (6%)	0
Wealth	13	11 (85%)	1 (8%)	0	1 (8%)
Distance	17	12 (71%)	5 (29%)	0	0

Table 3.3. Applicability of proposed candidate predictor variables for typical availability: Stage 1

Candidate predictor	Responses Total N = 23	Applicability, n (%) High	Moderate	Unlikely	Not at all
Clinical variables					
Vital Signs	19	14 (74%)	5 (26%)	0	0
Oxygen Saturation	18	7 (39%)	9 (50%)	2 (11%)	0
Height and weight	19	14 (74%)	5 (26%)	0	0
Vaccine history	19	6 (32%)	9 (47%)	4 (21%)	0
Antibiotic history	19	9 (47%)	7 (37%)	3 (16%)	0
Length of stay	19	17 (89%)	2 (11%)	0	0
Co-morbidities	19	12 (63%)	7 (37%)	0	0
Admit diagnosis	19	15 (79%)	4 (21%)	0	0
Discharge AMA	18	11 (61%)	5 (28%)	2 (11%)	0
Laboratory variables					
Hemoglobin level	17	9 (53%)	7 (41%)	1 (6%)	0
Blood culture	18	6 (33%)	6 (33%)	6 (33%)	0
Zinc level	13	8 (57%)	3 (21%)	2 (14%)	0
Social and demographic variables					
Age	17	15 (88%)	2 (12%)	0	0
Sex	17	16 (94%)	1 (6%)	0	0
Maternal education	17	11 (65%)	4 (24%)	2 (12%)	0
Wealth	12	7 (58%)	3 (25%)	1 (8%)	1 (8%)
Distance	16	12 (75%)	2 (13%)	2 (13%)	0

Table 3.4. Applicability of proposed candidate predictor variables for cost to measure: Stage 1

Candidate predictor	Responses Total N = 23	Applicability, n (%) High	Moderate	Unlikely	Not at all
Clinical variables					
Vital Signs	18	14 (78%)	2 (11%)	2 (11%)	0
Oxygen Saturation	18	5 (28%)	10 (56%)	3 (17%)	0
Height and weight	18	14 (78%)	3 (17%)	1 (6%)	0
Vaccine history	18	8 (45%)	7 (39%)	3 (17%)	0
Antibiotic history	18	9 (50%)	8 (44%)	1 (6%)	0
Length of stay	18	12 (67%)	3 (16%)	2 (11%)	1 (6%)
Co-morbidities	18	11 (61%)	5 (28%)	1 (6%)	1 (6%)
Admit diagnosis	18	13 (72%)	3 (17%)	2 (11%)	0
Discharge AMA	17	11 (65%)	3 (18%)	2 (12%)	1 (6%)
Laboratory variables					
Hemoglobin level	17	9 (53%)	6 (35%)	1 (6%)	1 (6%)
Blood culture	17	6 (35%)	6 (35%)	2 (29%)	0
Zinc level	14	2 (14%)	1 (7%)	9 (64%)	2 (14%)
Social and demographic variables					
Age	16	14 (88%)	1 (6%)	1 (6%)	0
Sex	16	13 (81%)	1 (6%)	1 (6%)	1 (6%)
Maternal education	16	11 (69%)	5 (31%)	0	0
Wealth	11	8 (72%)	2 (18%)	0	1 (9%)
Distance	15	11 (73%)	3 (20%)	1 (7%)	0

Table 3.5. Applicability of proposed candidate predictor variables for time and resources to measure: Stage 1

Candidate predictor	Responses Total N = 23	Applicability, n (%) High	Moderate	Unlikely	Not at all
Clinical variables					
Vital Signs	18	13 (72%)	4 (22%)	1 (6%)	0
Oxygen Saturation	18	10 (56%)	6 (33%)	2 (11%)	0
Height and weight	18	13 (72%)	5 (28%)	0	0
Vaccine history	18	8 (44%)	9 (50%)	1 (6%)	0
Antibiotic history	18	9 (50%)	7 (39%)	1 (6%)	1 (6%)
Length of stay	18	12 (67%)	4 (22%)	1 (6%)	1 (6%)
Co-morbidities	18	10 (56%)	5 (28%)	2 (11%)	1 (6%)
Admit diagnosis	18	12 (67%)	4 (22%)	2 (11%)	0
Discharge AMA	17	10 (59%)	4 (24%)	2 (11%)	1 (6%)
Laboratory variables					
Hemoglobin level	17	9 (59%)	6 (35%)	2 (12%)	0
Blood culture	17	6 (35%)	8 (47%)	2 (18%)	0
Zinc level	14	2 (14%)	2 (14%)	8 (57%)	2 (14%)
Social and demographic variables					
Age	16	14 (88%)	1 (6%)	1 (6%)	0
Sex	16	13 (81%)	2 (13%)	0	1 (6%)
Maternal education	16	11 (69%)	4 (25%)	1 (6%)	0
Wealth	11	7 (64%)	3 (27%)	1 (9%)	0
Distance	15	11 (73%)	3 (20%)	1 (7%)	0

Table 3.6. Proposed new variables for prediction, N=40

Clinical	**Laboratory**	**Social/Demographic**
Eating & drinking status	Blood glucose	Number of siblings
Mental Status	C-reactive protein	Number of parents present
Weight gain during admission	CBC with differential	Type of dwelling
Inputs and outputs	Chest X-ray	Water source
Breastfeeding success	HIV serology	Hygiene indicators
Urination in 12h prior to admit	CD4 count	Bednet use
Nutritional status	Blood gases	Cooking habits
HIV status	Ferritin	Maternal comorbidities
Antibiotic appropriateness	INR/PTT	Ethnicity
Time since last hospitalization	Lactate, pH, or serum bicarbonate	Social economic status
Time from referral to admission	Blood Urea Nitrogen	Sibling deaths
Length of illness	Serum Creatinine	Maternal birth spacing
Mid-upper arm circumference	Albumin	
Previous hospitalizations	CNS culture	

CBC = complete blood count

Table 3.7. Applicability of proposed candidate predictor variables as predictors: Stage 2

Candidate predictor	Responses	Applicability, n (%)			
	Total N = 13	High	Moderate	Unlikely	Not at all
Clinical variables					
Mental Status	10	8 (80%)	2 (20%)	0	0
Pre-admit urine freq.	10	6 (60%)	4 (40$)	0	0
Prior hospitalizations	10	4 (40%)	5 (50%)	1 (10%)	0
Time since last admit	10	2 (20%)	7 (70%)	1 (10%)	0
Duration of illness	10	6 (60%)	2 (20%)	2 (20%)	0
MUAC	8	3 (38%)	4 (50%)	1 (13%)	0
Prematurity	9	6 (67%)	3 (33%)	0	0
Laboratory variables					
Glucose	10	6 (60%)	3 (30%)	1 (10%)	0
Acidosis	10	6 (60%)	2 (20%)	1 (10%)	1 (10%)
Coagulation (INR/PTT)	10	2 (20%)	4 (40%)	3 (30%)	1 (10%)
Renal (BUN/SCr)	10	2 (20%)	7 (70%)	1 (10%)	0
Social and demographic variables					
Number of siblings	9	1 (11%)	6 (67%)	2 (22%)	0
Maternal co-morbidities	10	5 (50%)	5 (50%)	0	0
Maternal Age	9	3 (33%)	2 (22%)	4 (44%)	0
Parents live at home	9	4 (44%)	2 (22%)	3 (33%)	0
Sibling deaths	10	3 (30%)	6 (60%)	1 (10%)	0
Water source	9	7 (78%)	2 (22%)	0	0
Bednet use	8	4 (50%)	2 (25%)	2 (25%)	0

Table 3.8. Applicability of proposed candidate predictor variables for typical availability: Stage 2

Candidate predictor	Responses	Applicability, n (%)			
	Total N = 13	High	Moderate	Unlikely	Not at all
Clinical variables					
Mental Status	10	9 (90%)	1 (10%)	0	0
Pre-admit urine freq.	10	4 (40%)	4 (40%)	1 (10%)	1 (10%)
Prior hospitalizations	9	6 (67%)	3 (33%)	0	0
Time since last admit	9	3 (33%)	5 (56%)	1 (11%)	0
Duration of illness	9	8 (89%)	1 (11%)	0	0
MUAC	7	2 (29%)	4 (57%)	1 (14%)	0
Prematurity	9	4 (44%)	5 (56%)	0	0
Laboratory variables					
Glucose	9	5 (56%)	4 (44%)	0	0
Acidosis	9	3 (33%)	4 (44%)	2 (22%)	0
Coagulation (INR/PTT)	9	1 (11%)	5 (56%)	3 (33%)	0
Renal (BUN/SCr)	9	0	6 (67%)	3 (33%)	0
Social and demographic variables					
Number of siblings	8	3 (38%)	3 (38%)	2 (25%)	0
Maternal co-morbidities	9	2 (22%)	6 (67%)	1 (11%)	0
Maternal Age	8	5 (63%)	1 (13%)	2 (25%)	0
Parents live at home	8	5 (63%)	1 (13%)	3 (25%)	0
Sibling deaths	9	5 (56%)	4 (44%)	0	0
Water source	8	6 (75%)	1 (13%)	1 (13%)	0
Bednet use	7	5 (71%)	1 (14%)	1 (14%)	0

Table 3.9. Applicability of proposed candidate predictor variables for cost to measure: Stage 2

Candidate predictor	Responses	Applicability, n (%)			
	Total N = 13	High	Moderate	Unlikely	Not at all
Clinical variables					
Mental Status	9	7 (78%)	1 (11%)	1 (11%)	0
Pre-admit urine freq.	9	6 (67%)	2 (22%)	1 (11%)	0
Prior hospitalizations	9	6 (67%)	2 (22%)	1 (11%)	0
Time since last admit	9	5 (56%)	2 (22%)	1 (11%)	1 (11%)
Duration of illness	3	0	1 (11%)	1 (11%)	1 (11%)
MUAC	7	2 (29%)	4 (57%)	1 (14%)	0
Prematurity	9	5 (56%)	2 (22%)	1 (11%)	1 (11%)
Laboratory variables					
Glucose	9	4 (44%)	5 (56%)	0	0
Acidosis	9	2 (22%)	6 (67%)	1 (11%)	0
Coagulation (INR/PTT)	9	2 (22%)	4 (44%)	3 (33%)	0
Renal (BUN/SCr)	9	0	5 (56%)	4 (44%)	0
Social and demographic variables					
Number of siblings	8	5 (63%)	0	2 (25%)	1 (13%)
Maternal co-morbidities	9	4 (44%)	3 (33%)	1 (11%)	1 (11%)
Maternal Age	8	5 (63%)	0	2 (25%)	1 (13%)
Parents live at home	8	5 (63%)	0	2 (25%)	1 (13%)
Sibling deaths	9	6 (67%)	2 (22%)	0	1 (11%)
Water source	8	5 (63%)	1 (13%)	1 (13%)	1 (13%)
Bednet use	7	6 (86%)	0	1 (14%)	0

Table 3.10. Applicability of proposed candidate predictor variables for time and resources to measure: Stage 2

Candidate predictor	Responses	Applicability, n (%)			
	Total N = 13	High	Moderate	Unlikely	Not at all
Clinical variables					
Mental Status	9	7 (78%)	2 (22%)	0	0
Pre-admit urine freq.	9	4 (44%)	3 (33%)	1 (11%)	1 (11%)
Prior hospitalizations	9	6 (67%)	2 (22%)	1 (11%)	0
Time since last admit	9	4 (44%)	3 (33%)	1 (11%)	1 (11%)
Duration of illness	9	6 (67%)	1 (11%)	1 (11%)	1 (11%)
MUAC	7	1 (14%)	5 (71%)	1 (14%)	0
Prematurity	9	5 (56%)	3 (33%)	0	1 (11%)
Laboratory variables					
Glucose	9	4 (44%)	4 (44%)	1 (11%)	0
Acidosis	9	2 (22%)	6 (67%)	1 (11%)	0
Coagulation (INR/PTT)	9	2 (22%)	3 (33%)	4 (44%)	0
Renal (BUN/SCr)	9	0	5 (56%)	4 (44%)	0
Social and demographic variables					
Number of siblings	8	5 (63%)	0	2 (25%)	1 (13%)
Maternal co-morbidities	9	4 (44%)	3 (33%)	1 (11%)	1 (11%)
Maternal Age	8	5 (63%)	0	2 (25%)	1 (13%)
Parents live at home	8	5 (63%)	0	2 (25%)	1 (13%)
Sibling deaths	9	6 (67%)	1 (11%)	1 (11%)	1 (11%)
Water source	8	5 (63%)	1 (13%)	1 (13%)	1 (13%)
Bednet use	6	5 (83%)	0	1 (17%)	0

Table 3.11. Final list of candidate predictors for predictive model (N = 30)

Clinical	Laboratory	Social/demographic
Height	Hemoglobin	Bed net use
Weight	HIV status	Maternal age
Mid-upper arm circumference	Malaria blood smear	Maternal Education
Heart rate		Maternal HIV status
Respiratory rate		Maternal death
Systolic blood pressure		Number of siblings
Diastolic blood pressure		Sibling deaths
Temperature (axillary)		Distance (time)
Oxygen Saturation		Distance (cost)
Blantyre coma score		Availability of latrine
Immunization status		Water source
Prior antibiotic use		Boiling of drinking water
Prior antimalarial use		
Time since last hospitalization		
Duration of illness		

Table 4.1. 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%)
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 4.2. 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, never

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

Table 4.3. Models developed for prediction of 6 month post-discharge mortality

Variable	Regression Estimate	p-value	OR (95% CI)
Model 1 – Primary model, Intercept = 7.8497			
MUAC	-0.0471	<0.0001	0.95 (0.94 – 0.97)
SpO2	-0.0407	0.0031	0.96 (0.94 – 0.99)
Time since last hosp.	-0.2810	0.0080	0.76 (0.61 – 0.93)
HIV positive	0.9827	0.0171	2.67 (1.19 – 6.00)
Abnormal BCS	0.8774	0.0147	2.41 (1.19 – 4.87)
Model 2 – Model without SpO2, Intercept = 4.5294			
MUAC	-0.0506	<0.0001	0.95 (0.94 – 9.97)
Time since last hosp.	-0.2593	0.0120	0.77 (0.63 – 0.94)
HIV positive	1.1143	0.0048	3.05 (1.40 – 6.61)
Abnormal BCS	1.0549	0.0025	2.87 (1.45 – 5.67)
Model 3 – Model without MUAC, Intercept = 2.2858			
SpO2	-0.0454	0.0005	0.96 (0.93 – 0.98)
Time since last hosp.	-0.3179	0.0024	0.73 (0.59 – 0.89)
HIV positive	1.1533	0.0066	3.17 (1.34 – 7.29)
Abnormal BCS	0.9247	0.0098	2.52 (1.25 – 5.09)
WAZ	-0.3016	0.0001	0.74 (0.63 – 0.86)
Age	-0.0336	0.0038	0.97 (0.95 – 0.99)
Model 4 – Model without HIV, Intercept = 8.3221			
MUAC	-0.0494	<.0001	0.95 (0.94 – 0.97)
SpO2	-0.0422	0.0024	0.06 (0.93 – 0.99)
Time since last hosp.	-0.2991	0.0046	0.75 (0.61 – 0.93)
Abnormal BCS	0.8448	0.0191	2.28 (1.13 – 4.60)

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

Table 4.4. 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	0.81 (0.75 – 0.87)	0.035	80.0 (69.9 – 90.1)	64.8 (62.0 – 67.6)	10.7	98.4
2	0.81 (0.75 – 0.87)	0.037	80.3 (70.0 – 90.4)	64.5 (61.7 – 67.3)	10.7	98.6
3	0.80 (0.74 – 0.86)	0.031	80.0 (69.9 – 90.1)	57.9 (55.0 – 60.8)	9.1	98.1
4	0.80 (0.74 – 0.86)	0.034	80.0 (69.9 – 90.1)	62.0 (59.2 – 64.8)	9.9	98.3

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

Table 5.1. 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 (days), median (IQR)	3 (2 – 5)
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)
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)

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 5.2. Univariate hazard ratios for primary and secondary outcomes among discharged children

Variable	Death (n=61)		Death or Re-admission (n=245)	
	HR (95% CI)	p	HR (95% CI)	p
General Characteristics				
Sex (male)	0.90 (0.55 – 1.49)	0.69	1.04 (0.81 – 1.34)	0.78
Age <12 months	ref	.	ref	.
Age 12-24 months	0.66 (0.37 – 1.18)	0.16	0.69 (0.50 – 0.95)	0.02
Age > 24 months	0.38 (0.20 – 0.72)	0.003	0.77 (058 – 1.03)	0.08
Initial Referral	2.08 (1.19 – 3.63)	0.01	1.21 (0.93 – 1.59)	0.16
Discharge AMA	4.24 (2.44 – 7.34)	<0.0001	1.40 (0.94 – 2.07)	0.10
LOS <3 days	ref		ref	.
3-5 days	0.89 (0.45 – 1.79)	0.74	1.04 (0.78 – 1.39)	0.77
> 5 days	3.23 (1.78 – 5.89)	0.0001	1.19 (0.86 – 1.65)	0.31
Never hospitalized	ref	.	ref	.
< 7 days ago	3.41 (1.40 – 8.27)	0.007	2.60 (1.62 – 4.19)	<0.0001
7 – 30 days ago	2.25 (0.98 – 5.17)	0.06	1.85 (1.20 – 2.85)	0.005
30 days – 1 year	1.91 (1.05 – 3.48)	0.03	1.54 (1.13 – 2.10)	0.006
> 1 year ago	1.03 (0.30 – 3.55)	0.96	0.86 (0.52 – 1.43)	0.56
Anthropometric variables				
MUAC >125mm	ref	.	ref	.
MUAC <115mm	9.74 (5.71 – 16.61)	<0.0001	1.83 (1.25 – 2.68)	0.002
MUAC 115 – 125mm	2.66 (1.16 – 6.08)	0.02	1.14 (0.73 – 1.78)	0.57
WAZ > -2	ref	.	ref	.
WAZ < -3	4.58 (2.67 – 7.85)	<0.0001	0.97 (0.67 – 1.40)	0.85
WAZ -3 to -2	1.65 (0.75 – 3.61)	0.21	1.27 (0.88 – 1.83)	0.20
HAZ > -2	ref	.	ref	.
HAZ< -3	2.92 (1.61 - 5.29)	0.0004	0.91 (0.62 – 1.35)	0.65
HAZ -3 to -2	2.47 (1.31 – 4.65)	0.005	1.35 (0.96 – 1.89)	0.09
WHZ > -2	ref	.	ref	.
WHZ < -3	2.57 (1.42 – 4.67)	0.002	1.05 (0.75 – 1.47)	0.76
WHZ -3 to -2	2.38 (1.28 – 4.41)	0.006	1.15 (0.83 – 1.60)	0.41
Clinical Signs				
Tachycardia[¥]	0.56 (0.31 – 1.02)	0.06	0.92 (0.70 – 1.20)	0.57
Fast Breathing[¶]	1.67 (0.82 – 3.38)	0.16	1.29 (0.94 – 1.76)	0.12
Hypotension[§]	1.75 (0.79 – 3.84)	0.17	1.09 (0.67 – 1.75)	0.74
Temp 36 – 37.5^{o}C	ref	.	ref	.
Temp <36 ^{o}C	3.31 (1.15 – 9.53)	0.03	1.50 (0.73 – 3.08)	0.26
Temp 37.5 – 39 ^{o}C	0.87 (0.43 – 1.75)	0.69	1.06 (0.74 – 1.51)	0.75
Temp >39 ^{o}C	0.73 (0.35 – 1.53)	0.40	0.92 (0.64 – 1.33)	0.66
SpO2 95 – 100%	ref	.	ref	.
SpO2 <90%	3.23 (1.71 – 6.10)	0.0003	1.47 (1.10 – 1.98)	0.01
SpO2 90 – 95%	1.85 (0.94 – 3.63)	0.08	0.90 (0.66- 1.24)	0.52
Abnormal BCS	2.35 (1.28 – 4.34)	0.006	1.19 (0.81 – 1.74)	0.38
Hg >11g/dL	ref	.	ref	.
Hg 10 – 11 g/dL	1.42 (0.56 – 3.61)	0.46	1.29 (0.86 – 1.93)	0.21

Table 5.2. Cont.

Variable	Death (n=61)		Death or Re-admission (n=245)	
	HR (95% CI)	p	HR (95% CI)	p
Clinical Signs				
Hg 7 – 10 g/dL	2.47 (1.20 – 5.11)	0.01	1.16 (0.82 – 1.64)	0.39
Hg < 7 g/dL	1.66 (0.76 – 3.67)	0.21	1.40 (0.99 – 1.98)	0.06
Abnormal WBC	1.09 (0.66 – 1.80)	0.75	1.12 (0.88 – 1.45)	0.36
Illness >7days PTA	1.95 (1.18 – 3.22)	0.009	1.26 (0.97 – 1.62)	0.08
Diagnoses				
Pneumonia diagnosis	2.00 (1.21 – 3.31)	0.007	1.24 (1.04 – 1.74)	0.03
Malaria diagnosis	0.37 (0.21 – 0.66)	0.0006	0.79 (0.61 – 1.02)	0.07
Parasitemia	0.34 (0.17 – 0.69)	0.003	0.89 (0.67 – 1.16)	0.38
Gastroenteritis	0.83 (0.30 – 2.27)	0.71	0.81 (0.49 – 1.40)	0.41
HIV positive (vs neg)	4.70 (2.45 – 9.04)	<0.0001	1.47 (0.89 – 2.44)	0.14
Health behavior and social variables				
Bed net always	ref	.	ref	.
Bed net sometimes	1.17 (0.62 – 2.20)	0.63	0.89 (0.65 – 1.22)	0.47
Bed net never	1.17 (0.64 – 2.14)	0.61	0.95 (0.69 – 1.31)	0.73
Maternal ed. ≤ P3$^{\infty}$	ref	.	ref	.
Maternal ed. = P4 - P7	1.18 (0.63 – 2.21)	0.60	0.99 (0.73 – 1.34)	0.95
Maternal ed. = S1 - S6	0.73 (0.31 – 1.68)	0.45	0.84 (0.58 – 1.22)	0.35
Maternal ed. = PS	1.17 (0.42 – 3.25)	0.76	0.77 (0.44 – 1.36)	0.37
Distance < 30 min	ref	.	ref	.
Distance 30 – 60 min	0.70 (0.31 – 1.61)	0.40	0.89 (0.61 – 1.31)	0.56
Distance > 60 min	1.29 (0.71 – 2.34)	0.41	1.15 (0.85 – 1.56)	0.36
Number of children	1.02 (0.92 – 1.13)	0.76	1.03 (0.98 – 1.09)	0.20
Sibling deaths	1.51 (0.89 – 2.56)	0.13	1.27 (0.97 – 1.66)	0.08
Maternal HIV neg.	ref	.	ref	.
Maternal HIV pos.	1.75 (0.87 – 3.49)	0.12	1.22 (0.82 -1.80)	0.32
Maternal HIV unk.	1.27 (0.65 – 2.47)	0.48	1.00 (0.70 – 1.43)	1.00
Maternal Age (years)	1.00 (0.97 – 1.04)	0.91	0.96 (0.98 – 1.01)	0.59
Municipal water use	ref	.	ref	.
Protected spring use	1.51 (0.64 – 3.55)	0.35	1.02 (0.61 – 1.69)	0.94
Bore hole use	0.97 (0.36 – 2.56)	0.94	1.30 (0.82 – 2.06)	0.27
Fast stream use	0.69 (0.09 – 5.11)	0.71	1.43 (0.69 – 2.95)	0.33
Slow stream use	0.39 (0.05 – 2.89)	0.36	0.49 (0.20 – 1.20)	0.12
Shallow well	1.05 (0.59 – 1.88)	0.86	1.20 (0.90 – 1.59)	0.22
Boil all drinking water	0.81 (0.48 – 1.38)	0.44	0.95 (0.72 – 1.25)	0.71

¥ >180bpm if age < 24 months, >140bmp if age >24 months; ¶ >50 if age <12 months, >40 if age >12 months; § Systolic blood pressure z-score < -2; ∞ Maternal education divided into ≤ primary 3, primary 4 – 7, any secondary, any post-secondary; AMA = against medical advice; LOS = length of stay; MUAC = mid upper arm circumference; WAZ = weight for age z-score; HAZ = height/length for age z-score; WHZ = weight for height/length z-score; BCS = Blantyre coma score; WBC = white blood cell count; PTA = prior to admission

Table 5.3. Principal component regression results, unadjusted and adjusted p-values

PC	Component loadings	Unadjusted p	Adjusted p
Primary outcome - mortality			
1	MUAC, weight for age z, weight for length z	0.002	0.11
2	Weight for age z, height for age z	0.004	0.05
5	MUAC, age	0.01	0.03
9	Length of index admission	0.03	0.23
10	Duration of illness	0.09	0.19
12	SpO2	0.003	0.009
17	Time since last hospitalization	0.006	0.01
18	Blantyre coma score	0.009	0.001
20	Discharge against medical advice	<.0001	0.0002
26	HIV	0.0002	0.001
30	Clinical malaria	0.08	0.09
32	MUAC	<.0001	<.0001
Secondary outcome – mortality or readmission			
8	Hemoglobin level	0.05	0.49
12	SpO2	0.04	0.002
17	Time since last hospitalization	<0.0001	0.004

MUAC = mid-upper arm circumference

Table 6.1. Structured interview questionnaire and probes

1. Tell me about the events leading up to the death of your child? Give as many details as many details as you can think of.
    - What happened?
    - What were the initial symptoms and how did the illness progress?
2. Did you think of seeking care for your child?
3. What were the barriers/difficulties/challenges that prevented you (the parents/guardians) from going to the hospital/health facility to seek care?
4. Where exactly did the child die?
    - For instance, on the way to or at the hospital/health centre, at home, local clinic, another person's home (aunt, grandmother etc.) or with traditional healer.
5. Where was the child staying just prior to death?
    - Who was looking after the child at the time of becoming sick?
6. Did you (or the person caring for the child) notice that your child was very sick on this occasion?
    - If no, did your child appear healthy/well or like usual?
    - If yes, what were the things you noticed as being the signs your child was very sick?
7. What were the barriers/difficulties/challenges that prevented you (the parents/guardians) from going to the hospital/health facility to seek care?
8. Could anything have been done to help you or your child?
    - If yes, in your opinion, what could have been done?

Table 6.2. Participant characteristics

Variable	**Mean ± SD or N (%)**
Age (months)	19.2 ± 14.2
Gender	
Male	22 (55.0%)
Female	18 (45.0%)
Distance to hospital	
< 30 minutes	6 (15.0%)
30 minutes – 1 hour	7 (17.5%)
> 1 hour	27 (67.5%)
HIV status	
Child HIV+	7 (17.5%)
Maternal HIV+	6 (15.0%)
Maternal age (years)	29.0 ± 7.25
Maternal education	
< Primary 3	12 (30.0%)
Primary 3 – Primary 7	22 (55.0%)
Secondary	5 (12.5%)
Post-secondary	1 (2.5%)
Water supply	
Municipal water	6 (15.0%)
Protected spring	4 (10.0%)
Bore hole	6 (15.0%)
Fast running stream	1 (2.5%)
Slow stream	1 (2.5%)
Shallow well	21 (52.5%)
Bed net use (child)	
Always	15 (37.5%)
Sometimes	12 (30.0%)
Never	13 (32.5%)

Table 6.3. Predictors of out of hospital death among children who died post-discharge

Variable	OR (95% CI)	p-value
Sex (ref = male)	1.10 (0.38 – 3.19)	0.86
Age (per 1 month increase)	1.04 (0.99 – 1.10)	0.12
HIV Positive	1.33 (0.31 – 5.86)	0.70
Bed net use (ref = always)		
Sometimes	6.40 (1.22 – 33.47)	0.03
Never	8.00 (1.56 – 41.03)	0.01
Maternal Education (ref = < P3)		
P4 - P7	0.35 (0.07 – 1.87)	0.22
S1 - S6	0.19 (0.03 – 1.40)	0.10
Post-secondary	0.04 (0.00 – 0.54)	0.02
Maternal Education (per category increase)	0.38 (0.19 – 0.79)	0.009
Distance (ref = <30 minutes)		
30 – 60 minutes	4.00 (0.62 – 25.96)	0.15
> 60 minutes	3.20 (0.92 – 11.12)	0.07
Maternal HIV status (ref = negative)		
Positive	1.38 (0.32 – 6.05)	0.67
Unknown	1.21 (0.27 – 5.42)	0.80
Water source (ref = municipal water)		
Protected spring	12.00 (1.20 – 120.08)	0.03
Bore hole	8.00 (0.75 – 85.73)	0.09
Fast running stream	NA	NA
Slow stream	NA	NA
Shallow well	10.50 (2.58 – 42.68)	0.001
Early death (ref=<30days)	1.92 (0.65 – 5.68)	0.24
Discharged against medical advice	1.05 (0.33 – 3.33)	0.95
Length of Stay (ref =<3 days)		
3-5 days	1.15 (0.24 – 5.39)	0.86
> 5 days	0.72 (0.20 – 2.59)	0.61

Table 6.4. Illustrative quotes of barriers to care identified through survey

Barriers to Care	**Quote**
Monetary constraints	*I took her to the nearby clinic and was seen by a nurse who referred us to the hospital. However, due to lack of money, I went back home.*
Transportation	*The cars in this place travel at night, starting from midnight to 5 am. Before that time, the only option is hiring which was too expensive for us, so this caused a delay to reach the hospital.*
No paternal support	*The father told me that I should let the child die.*
Recent hospital visit	*I only delayed to take him to the hospital because I thought that maybe the sickness was the effect of drugs he had received in the hospital… but he kept getting worse.*
No notable improvement	*As for Kabuyanda Health Center, which was near me, I had been going there with no improvement, so I did not see any need to go back.*

Table 7.1. Baseline characteristics of study subjects

Characteristic	Frequency/mean/median Total N=717
Demographics	
Median age in months (IQR)	25 (11 – 64)
Male sex	360 (50.2%)
History of sibling death	20.8%
Ever breastfed	99.9%
Median number of Children in Family (IQR)	3.0 (2.0 – 5.0)
Mother Alive	700 (97.6%)
Maternal HIV positive	35 (4.9%)
Maternal HIV negative	575 (80.2%)
Maternal HIV unknown	107 (14.9%)
HIV status	
Known HIV positive	5 (0.7%)
Maternal education	
No education	93 (13.0%)
Less than Grade 3	78 (10.9%)
Grade 3 to Grade 7	380 (53.0%)
Some Secondary School (S1 to S6)	133 (18.6%)
Post-Secondary	33 (4.6%)
Transport cost	
≤ 1000 UGX (1000 UGX = 0.4 USD)	144 (20.1%)
1001 – 2000 UGX	261 (36.4%)
2001 – 3000 UGX	175 (24.4%)
> 3000 UGX	137 (19.1%)
Bednet use	
Never	139 (19.4%)
Sometimes	54 (7.5%)
Always	524 (73.1%)
Distance to health center (typical transport)	
< 30 min	539 (75.2%)
30 – 60 minutes	156 (21.8%)
> 60 minutes	22 (3.1%)
Duration of illness prior to visit	
< 7 days	524 (73.2%)
7-30 days	153 (21.4%)
> 30 days	39 (5.5%)
Seen by CHW	177 (24.7%)
Referred by CHW	134 (18.7%)
Clinical variables	
Mean RR (SD)	38.2 (14.6)
Mean HR age Z score (SD)	1.1 (0.95)
Mean RR age Z score (SD)	1.9 (2.6)
Mean SBP age Z score (SD)	0.55 (3.17)
Mean weight for age Z score (SD)	-0.44 (1.47)
Mean Temperature (SD)	37.1 (1.03)
Median SpO2 (IQR)	97.3 (95.1 – 98.5)

CHW: Community health worker; RR: Respiratory Rate; HR: Heart Rate; SBP: Systolic blood pressure

Table 7.2. Outpatient department diagnoses

Outpatient/Admitting diagnosis	**Frequency n (%) Total N=717**
Respiratory tract infection (not specified)	264 (36.8%)
Malaria	221 (30.1%)
Pneumonia	164 (22.9)
Skin and Soft Tissue Infection	38 (5.3%)
Gastroenteritis	40 (5.6%)
HIV	4 (0.6%)
Tuberculosis	2 (0.3%)
Meningitis/Encephalitis	0 (0%)
Other infection	72 (10.0%)
Other non-infectious diagnosis	419 (58.4%)

Table 7.3. Outcomes of subjects during SCV and during 30 day follow-up period

Event Details	**Frequency n (%)**
Immediate events (Total N=717)	
Outcome event*	85 (11.9%)
Death	0 (0%)
Immediate admission	72 (10.1%)
Referral	16 (2.2%)
30 day follow-up events (Total N=604)	
Outcome event*	47 (7.8%)
Death during 30 day follow-up	3 (0.5%) (2 at home, 1 in hospital)
Admission post-OPD visit	8 (1.3%)
CHW visit post-OPD visit	8 (1.3%)
Physician/Clinical officer visit post-OPD visit	19 (3.2%)
Nurse visit post-OPD visit	3 (0.5%)
Traditional healer visit post-OPD visit	0 (0%)
Untrained health worker visit post-OPD visit	10 (1.7%)

* Number is lower than sum of individual events since due to event overlap

Table 7.4. Univariate association between baseline variables and immediate and early events

Variable	Immediate events OR (95% CI) Total N=717	Events within 30 days OR (95% CI) Total N=604
Demographic variables		
Male sex	1.26 (0.80 – 1.99)	1.69 (0.92 – 3.11)
Age (ref = <12months)	ref	ref
Age 12-24 months	1.15 (0.62 – 2.13)	1.00 (0.40 – 2.27)
Age 24 – 60 months	1.30 (0.72 – 2.33)	0.91 (0.40 – 2.06)
Age > 60 months	0.45 (0.22 – 0.94)	0.78 (0.34 – 1.77)
Transport costs (ref = ≤1k)		
1-2k	0.74 (0.37 – 1.45)	1.16 (0.52 – 2.55)
2-3k	1.15 (0.58 – 2.28)	0.97 (0.41 – 2.33)
>3k	1.79 (0.91 – 3.51)	0.57 (0.19 – 1.72)
Distance to health center (Ref = <30 min)		
30-60min	1.92 (1.16 – 3.17)	0.76 (0.35 – 1.67)
>60 min	2.70 (0.96 – 7.61)	0.62 (0.08 – 4.75)
Sibling deaths	0.53 (0.27 – 1.03)	0.72 (0.33 – 1.58)
Number of siblings (ref = ≤1)		
2-3	0.90 (0.53 – 1.54)	0.55 (0.25 – 1.21)
≥ 4	0.60 (0.34 – 1.06)	0.80 (0.41 – 1.58)
Maternal Education (ref = no education)		
Less than P3	0.95 (0.35 – 2.53)	0.52 (0.16 – 1.75)
P4-P7	1.34 (0.66 – 2.76)	0.51 (0.23 – 1.12)
≥S1	0.76 (0.33 – 1.80)	0.56 (0.23 – 1.39)
Maternal HIV status (ref = negative)		
HIV positive	1.54 (0.62 – 3.85)	0.89 (0.20 – 3.87)
HIV unknown	0.85 (0.43 – 1.68)	1.12 (0.48 – 2.60)
Health seeking/behavior variables		
Bednet use (ref = never)		
Sometimes	1.33 (0.51 – 3.50)	0.61 (0.07 – 5.62)
Always	1.24 (0.67 – 2.29)	2.87 (1.01 – 8.19)
Antibiotic prior to visit	1.03 (0.65 – 1.65)	1.19 (0.65 – 2.18)
Antimalarial prior to visit	2.17 (1.36 – 3.45)	0.75 (0.38 – 1.52)
CHW referral	1.51 (0.88 – 2.57)	0.81 (0.35 – 1.86)
Seen by CHW	2.03 (1.26 – 3.27)	0.70 (0.33 – 1.50)
Clinical variables		
Duration of illness (Ref = <7days)		
7-30 days	1.47 (0.88 – 2.45)	0.84 (0.39 – 1.80)
> 30 days	0.43 (0.10 – 1.81)	1.28 (0.37 – 4.45)
Raw RR	1.03 (1.01 – 1.04)	1.00 (0.98 – 1.02)
RR age z-score	1.09 (0.01 – 1.17)	1.00 (0.89 – 1.13)
Raw HR	1.02 (1.01 – 1.03)	1.00 (0.99 – 1.01)
HR age z-score	1.23 (1.07 – 1.42)	1.00 (0.83 – 1.19)
Raw SBP	0.98 (0.97 – 1.00)	1.02 (0.99 – 1.04)
SBP age z-score	0.96 (0.85 – 1.08)	1.27 (1.05 – 1.54)
Temperature (above 36.5) as cont. variable Per 1^{O}C increase	2.02 (1.57 – 2.57)	0.68 (0.43 – 1.07)
Temperature (below 36.5) as cont. variable per 1^{O}C decrease	1.13 (0.35 – 3.62)	2.04 (0.77 – 6.07)
SpO2 (per 1% decrease)	1.06 (1.02 – 1.09)	1.02 (0.98 – 1.07)

Table 7.4. Continued.

Variable	Immediate events OR (95% CI) Total N=717	Events within 30 days OR (95% CI) Total N=604
WAZ (ref = >-2)	ref	ref
WAZ -2 to WAZ -3	1.16 (0.53 – 2.55)	1.03 (0.35 – 3.00)
WAZ <-3	2.72 (1.27 – 5.81)	1.76 (0.59 – 5.28)
Presence of immediate event	NA	1.10 (0.45 – 2.71)
Diagnostic variables (adjusted*)		
Gastroenteritis	0.75 (0.17 – 3.40)	1.03 (0.25 – 4.69)
Clinical malaria	4.50 (2.44 – 8.30)	0.90 (0.41 – 1.00)
Pneumonia	4.13 (2.01 – 8.15)	1.80 (0.66 – 4.94)
Other respiratory tract infection	0.13 (0.04 – 0.40)	1.31 (0.46 –3.70)
SSTI	0.63 (0.12 – 3.18)	1.69 (0.38 – 7.39)
Other infection	0.47 (0.13 – 1.64)	1.30 (0.39 – 4.36)
Non infection (other)	1.58 (0.69 – 3.62)	0.99 (0.30 – 3.28)

*adjusted for other diagnoses due to overlapping diagnoses

WAZ = weight for age z-score; SSTI = skin and soft tissue infection; RR = respiratory rate; HR = heart rate; SBP = systolic blood pressure; CHW = community health worker

Table 7.5. Comparison of baseline characteristics of those followed-up and those lost to follow-up

Characteristic	Followed-up Frequency/mean/median Total N=604	Lost to follow-up Frequency/mean/median Total N=113	P-value
Demographics			
Median age (IQR)	25 (12-68)	23 (10-48)	0.10
Male sex	49.8	52.2	0.6
Sibling death	21.7	15.9	0.16
Median children in family (IQR)	3 (2-5)	3 (2-4)	0.03
Mother alive	2.3	2.6	0.80
Transport			
Maternal HIV status			0.058
Maternal HIV+	4.8	5.3	
Maternal HIV-	81.6	72.6	
Maternal HIV unknown	13.6	22.1	
Maternal education			0.05
No education	13.1	12.4	
Less than Grade 3	9.4	18.6	
Grade 3 – Grade 7	53.3	51.3	
Secondary School (S1-S6)	19.5	13.3	
Post-Secondary	4.6	4.4	
Transport costs			0.058
≤ 1000 UGX	20.7	16.8	
1001 – 2000 UGX	36.3	37.2	
2001 – 3000 UGX	25.5	18.6	
> 3000 UGX	17.6	27.4	
Bednet use			0.72
Never	18.9	22.1	
Sometimes	7.6	7.1	
Always	73.5	70.8	
Distance from health center			0.28
< 30 min	76.2	69.9	
30 – 60 minutes	20.7	27.4	
> 60 minutes	3.15	2.7	
Duration of illness prior to visit			0.30
< 7 days	73.0	74.3	
7-30 days	22.1	17.7	
> 30 days	5.0	8.0	
Clinical variables			
Mean RR (SD)	37.6 (14.7)	41.3 (13.8)	0.01
Mean RR age z-score (SD)	2.3 (3.1)	1.8 (2.5)	0.05
Mean HR age z-score (SD)	1.1 (1.7)	1.3 (1.6)	0.36
Mean SBP age z-score (SD)	0.5 (1.4)	1.1 (7.3)	0.06
Mean WAZ (SD)	-0.45 (1.5)	-0.40 (1.6)	0.80
Mean temperature (SD)	37.1 (1.0)	37.2 (1.0)	0.15
Median SpO2	97.5 (95.3 – 98.6)	96.4 (94.0 – 98.2)	0.007

RR = respiratory rate; HR = heart rate; SBP = systolic blood pressure; WAZ = weight for age z-score; SpO2 = oxygen saturation

Table 8.1a. Definition of sepsis

Systemic inflammatory response syndrome (SIRS)
Presence of at least 2 of the following, one of which must be abnormal temperature or leukocyte count
Core temperature > 38.5ºC or < 36ºC
Tachycardia or Bradycardia (see below) in the absence of external stimulus, drugs etc.
Tachypnea (see below) not related to underlying neuromuscular disease or anesthesia
Leukocyte count elevated or depressed (see below)
Infection
Suspected or proven infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection

Table 8.1b. Age-specific cut-offs for heart rate, respiratory rate and leukocyte count

Age group	**Heart Rate, Beats/Min**		**Respiratory Rate, Breaths/Min**	**Leukocyte Count x 10^3/mm^3**
	Tachycardia	**Bradycardia**		
1 mo – 1 yr	> 180	< 90	> 34	> 17.5 or < 5
2 yr – 5 yr	> 140	N/A	> 22	> 15.5 or < 6

Table 8.2. Characteristics of subjects (n=1307)

General characteristics	**Frequency, n (%)**
Age (months), median (IQR)	18 (11-34)
Male sex	717 (54.9)
Length of stay (days), median (IQR)	3 (2 – 5)
Discharge AMA	120 (9.7)
Duration of illness < 7 days	841 (64.3)
Final diagnoses	
Pneumonia	410 (31.4)
Clinical malaria	659 (50.4)
Parasitemia	434 (33.5)
Gastroenteritis	102 (7.8)
Meningitis	39 (3.0)
Comorbidities	
HIV	66 (5)
Tuberculosis	23 (1.8)
Anthropometrics	
Underweight (WAZ <-2)	372 (28.6)
Severe underweight (WAZ <-3)	206 (15.9)
Wasting (WHZ <-2)	454 (35.3)
Severe Wasting (WHZ <-3)	237 (18.4)
Stunting (HAZ < -2)	368 (28.5)
Severe Stunting (HAZ < -3)	185 (14.3)
MUAC < 125	187 (14.5)
MUAC < 115	94 (7.3)
Distance from hospital	
< 30 minutes	339 (25.9)
30 minutes – 1 hour	290 (22.2)
> 1 hour	678 (51.9)

Table 8.3. Characteristics of individual criteria for SIRS and sepsis in study sample

Criteria	n (%) N = 1307	Sensitivity* (95% CI)	Specificity* (95% CI)	PPV (%)	NPV (%)
WBC criteria only	587 (45.2)	0.72 (0.61 – 0.83)	0.56 (0.53 – 0.59	7.8	97.5
Temp. criteria only	1042 (79.7)	0.86 (0.78 – 0.95)	0.21 (0.18 – 0.23)	5.4	96.6
Heart rate criteria only	453 (34.7)	0.38 (0.25 – 0.50)	0.66 (0.63 – 0.68)	5.3	95.3
RR criteria only	1246 (95.4)	0.94 (0.88 – 1.0)	0.05 (0.03 – 0.06)	4.8	93.3
Sepsis (WBC + Temp.)	478 (36.8)	0.59 (0.47 – 0.72)	0.64 (0.62 – 0.67)	8.0	96.8
Sepsis (WBC + HR)	219 (16.9)	0.27 (0.16 – 0.38)	0.84 (0.82 – 0.86)	7.8	95.7
Sepsis (WBC + RR)	572 (44.1)	0.68 (0.56 – 0.80)	0.57 (0.54 – 0.60)	7.5	97.3
Sepsis (Temp. + HR)	399 (30.6)	0.33 (0.21 – 0.45)	0.70 (0.67 – 0.72)	5.3	95.3
Sepsis (Temp. + RR)	1001 (76.7)	0.81 (0.71 – 0.91)	0.23 (0.21 – 0.26)	5.2	96.1
Sepsis (Full definition)	1121 (85.9)	0.95 (0.90 – 1.0)	0.15 (0.13 – 0.17)	5.4	98.4

* The sensitivity and specificity refer to the proportion of deaths captured and the proportion of survivors captured by each of the individual SIRS and sepsis criteria, respectfully.
PPV = positive predictive value; NPV = negative predictive value; WBC = leukocyte count; Temp. = axillary temperature; HR = heart rate; RR = respiratory rate

Table 8.4. Final diagnoses among those who died as reported by medical team (N = 65)

Diagnosis	**n* (%)**
Malaria	27 (41)
Pneumonia	19 (29)
Diarrhea	7 (11)
Meningitis	7 (11)
No infection	2 (3)
Sepsis (source not defined)	8 (12)
TB	2 (3)
Measles	1 (1.5)
Any combination	7 (11)

* numbers add to more than 65 due to overlapping diagnoses in some study subjects

Table 8.5. Characteristics of subjects who died but did not meet sepsis criteria

Subject	**LOS**	**HR**	**Temp**	**RR**	**BCS**	**WBC**	**HIV**	**SpO2**	**Dx**
1	0	114	38.2	11	2	13.0	Negative	62%	Meningitis, malnutrition, bowel obstruction
2	2	160	37.0	75	5	15.0	Positive	98%	Pneumonia
3	4	154	36.8	26	5	22.8	Exposed	97%	Diarrhea

LOS: Length of stay (days), HR: Heart rate, Temp: Axillary temperature (^{o}C), BCS: Blantyre coma score, WBC: Leukocyte count (x 10^{9}/L), Dx: Final diagnosis

Table 9.1. Characteristics of subjects (n=1307)

General characteristics	**Frequency, n (%)**
Age < 12m	393 (30.1)
Age 12m – 24m	402 (30.8)
Age 24m – 36m	210 (16.1)
Age 36m - 48m	159 (12.2)
Age > 48m	142 (10.9)
Female sex	590 (45.1)
Length of stay (days), median (IQR)	3 (2 – 5)
Discharge AMA	120 (9.7)
Duration of illness < 7 days	841 (64.3)
Final diagnoses	
Pneumonia	410 (31.4)
Clinical malaria	659 (50.4)
Parasitemia	434 (33.5)
Gastroenteritis	102 (7.8)
Meningitis	39 (3.0)
Comorbidities	
HIV	66 (5)
Tuberculosis	23 (1.8)
Anthropometrics	
Underweight (WAZ <-2)	372 (28.6)
Severe underweight (WAZ <-3)	206 (15.9)
Wasting (WHZ <-2)	454 (35.3)
Severe Wasting (WHZ <-3)	237 (18.4)
Stunting (HAZ < -2)	368 (28.5)
Severe Stunting (HAZ < -3)	185 (14.3)
MUAC < 125mm	187 (14.5)
MUAC < 115mm	94 (7.3)
Distance from hospital	
< 30 minutes	339 (25.9)
30 minutes – 1 hour	290 (22.2)
> 1 hour	678 (51.9)

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 9.2. Univariate analyses of candidate predictor variables for inpatient-mortality

Variable	n (%)	OR (95% CI)	p-value	AUC ROC (95% CI)
Age (months)	1306 (99.9)	1.00 (0.99 - 1.02)	0.852	0.51 (0.44 - 0.58)
Sex (female)	1307 (100)	0.96 (0.58 - 1.58)	0.866	0.51 (0.44 - 0.57)
MUAC	1293 (98.9)	0.98 (0.96 - 0.99)	<0.001	0.60 (0.53 - 0.68)
Weight	1300 (99.5)	0.89 (0.81 - 0.97)	0.008	0.59 (0.52 - 0.67)
Weight-age z-score	1299 (99.4)	0.75 (0.65 - 0.87)	<0.001	0.64 (0.56 - 0.71)
Weight-length z-score	1282 (98.1)	0.80 (0.72 - 0.89)	<0.001	0.63 (0.55 - 0.7)
Height-age z-score	1286 (98.4)	0.90 (0.80 - 1.00)	0.052	0.57 (0.50 - 0.64)
BMI-age z-score	1282 (98.1)	0.81 (0.71 - 0.92)	<0.001	0.62 (0.54 - 0.69)
Heart rate	1306 (99.9)	0.99 (0.98 - 1.00)	0.04	0.55 (0.47 - 0.63)
Heart rate z-score	1305 (99.8)	0.87 (0.76 - 1.00)	0.051	0.53 (0.45 - 0.62)
Resp. rate	1306 (99.9)	1.01 (1.00 - 1.03)	0.17	0.56 (0.49 - 0.64)
Resp. rate age z-score	1305 (99.8)	1.06 (1.00 - 1.12)	0.063	0.55 (0.48 - 0.63)
SBP	1298 (99.3)	0.98 (0.96 - 0.99)	0.01	0.60 (0.53 - 0.68)
SBP z-score	1277 (97.7)	0.84 (0.70 - 1.00)	0.045	0.59 (0.51 - 0.67)
DBP	1298 (99.3)	0.96 (0.94 - 0.98)	<0.001	0.65 (0.58 - 0.73)
Transformed SpO2	1291 (98.8)	1.03 (1.01 - 1.05)	<0.001	0.59 (0.50 - 0.68)
Temperature – raw	1307 (100)	0.68 (0.57 - 0.80)	<0.001	0.61 (0.54 - 0.68)
Temperature – transformed	1307 (100)	1.05 (0.93 - 1.18)	0.466	0.50 (0.43 - 0.57)
Blantyre coma score	1307 (100)	0.09 (0.05 - 0.15)	<0.001	0.73 (0.67 - 0.79)
Hemoglobin (g/dL)	1299 (99.4)	0.94 (0.87 - 1.02)	0.157	0.56 (0.48 - 0.64)
Parasitemia (ref: neg)	1297 (99.2)	0.65 (0.36-1.16)	0.144	0.54 (0.49-0.6)
SR Maternal HIV (ref: neg)	1087 (83.2)	1.91 (0.93-3.95)	0.079	0.55 (0.48-0.61)
HIV status (ref: neg)	1263 (96.6)	5.02 (2.22-11.38)	<0.001	0.58 (0.51-0.64)

MUAC: mid-upper arm circumference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SR: Self report

Table 9.3. Model characteristics

Model	AUC (95% CI)	Sens. (95% CI)	Spec. (95% CI)	PPV (95% CI)	NPV (95% CI)
1	0.85 (0.80 - 0.89)	0.83 (0.74 - 0.92)	0.76 (0.73 - 0.78)	0.15 (0.11 - 0.19)	0.99 (0.98 - 1.00)
2	0.84 (0.79 - 0.89)	0.80 (0.70 - 0.90)	0.76 (0.74 - 0.79)	0.15 (0.11 - 0.19)	0.99 (0.98 - 1.00)
3	0.82 (0.72 - 0.91)	0.82 (0.72 - 0.91)	0.71 (0.68 - 0.73)	0.13 (0.10 - 0.16)	0.99 (0.98 - 0.99)

PPV: Positive predictive value, NPV: Negative predictive value

Table 9.4. Models developed for prediction of in-patient mortality

Variable	Regression Estimate	p-value	OR (95% CI)
Model 1 – Primary model, Intercept = -4.280			
Abnormal BCS	2.51	<0.001	12.30 (7.10 - 21.30)
Positive HIV diagnosis	1.32	0.007	3.74 (1.46 - 9.57)
Weight-age z-score	-0.25	0.002	0.78 (0.66 - 0.91)
Model 2 – Model without weight for age z-score, Intercept =-0.523			
Abnormal BCS	2.54	<0.001	12.68 (7.31 - 22.01)
Positive HIV diagnosis	2.27	0.006	3.79 (1.48 - 9.71)
MUAC (mm)	-0.03	0.002	0.98 (0.96 - 0.99)
Model 3 – Model without HIV and weight for age z-score, Intercept = 0.303			
Abnormal BCS	2.47	<0.001	11.78 (6.90 - 20.13)
MUAC (mm)	-0.03	<0.001	0.97 (0.96 - 0.99)

BCS: Blantyre coma score, MUAC: Mid-upper arm circumference

Figures

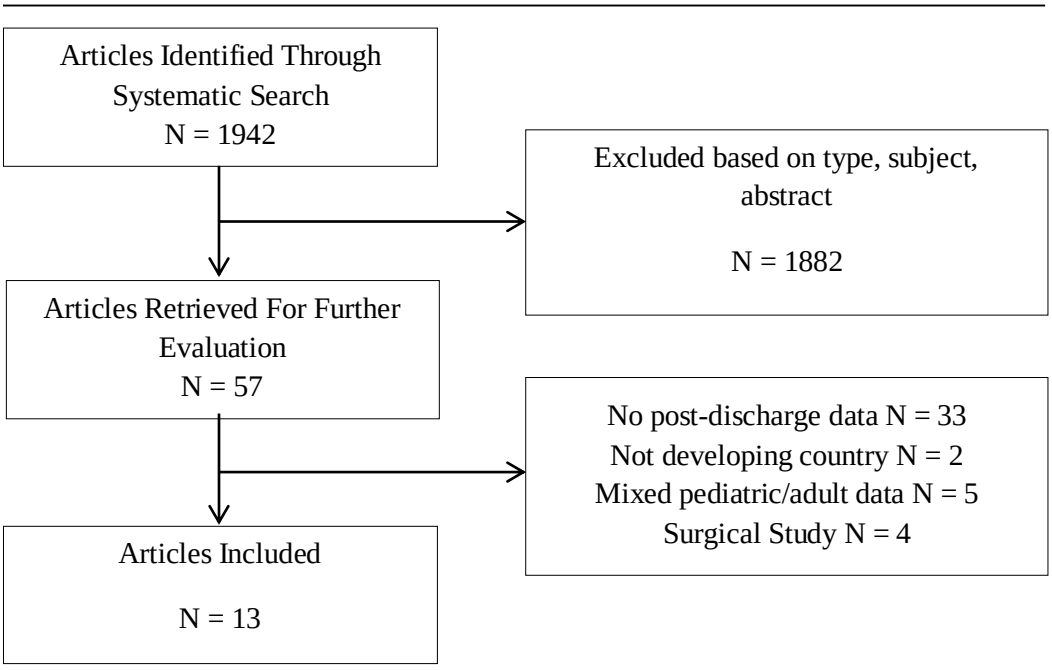

Figure 2.1. Flow diagram of search

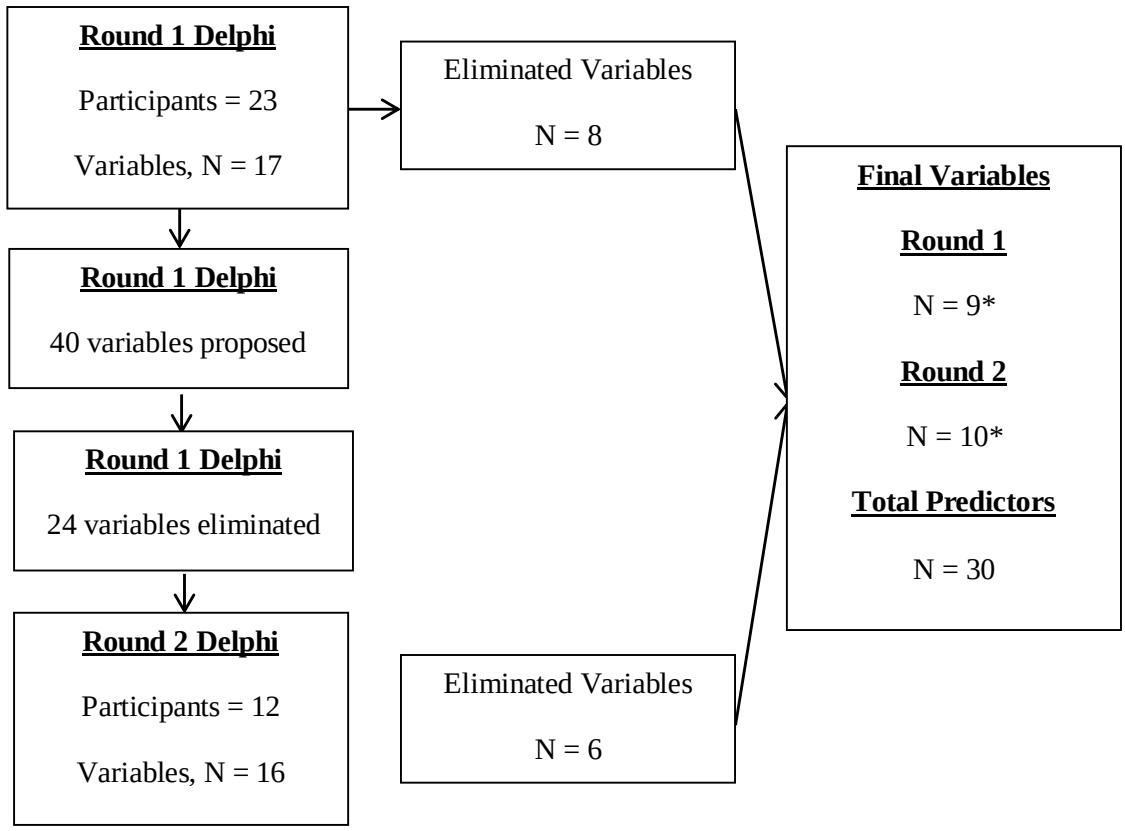

Figure 3.1. Flow diagram of Delphi process.

* Variables included some with multiple predictors listed as single variables (eg. height/weight and vital signs). Total predictors are therefore not a sum of final variables from Round 1 and Round 2 of Delphi process.

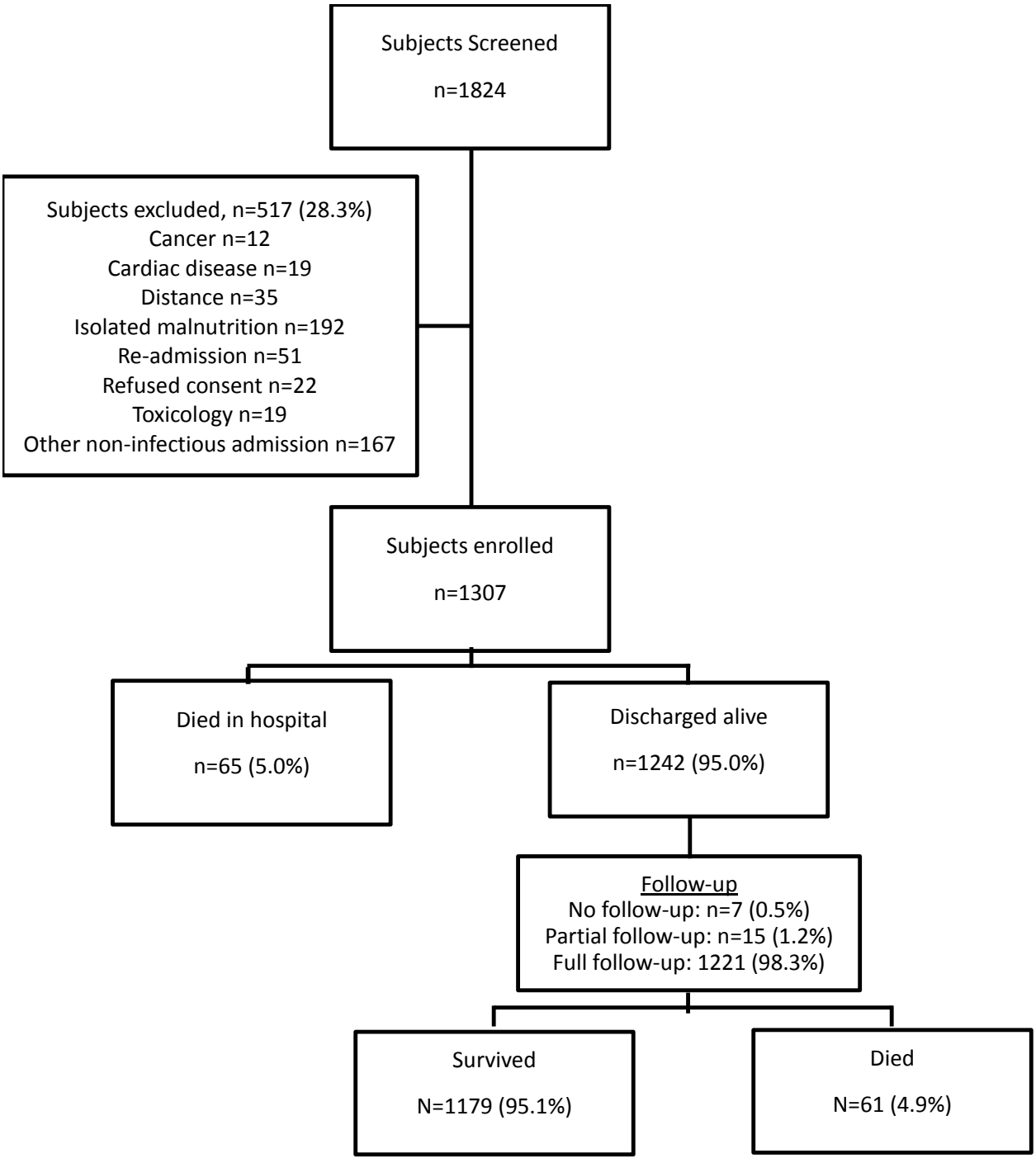

Figure 4.1. Consort diagram of study flow

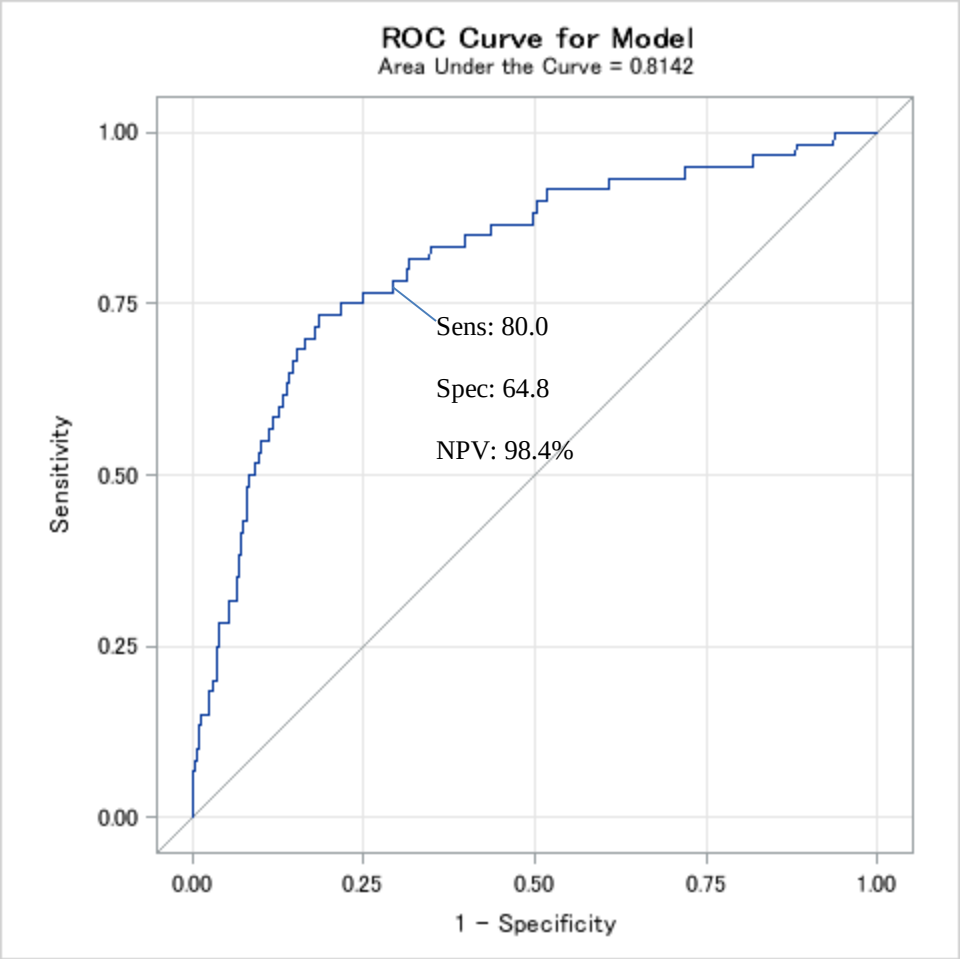

Figure 4.2. Performance of the primary prediction model derived with data from admission. ROC = receiver operating characteristic. Sens = sensitivity. Spec = specificity. NPV = negative predictive value. PPV = positive predictive value.

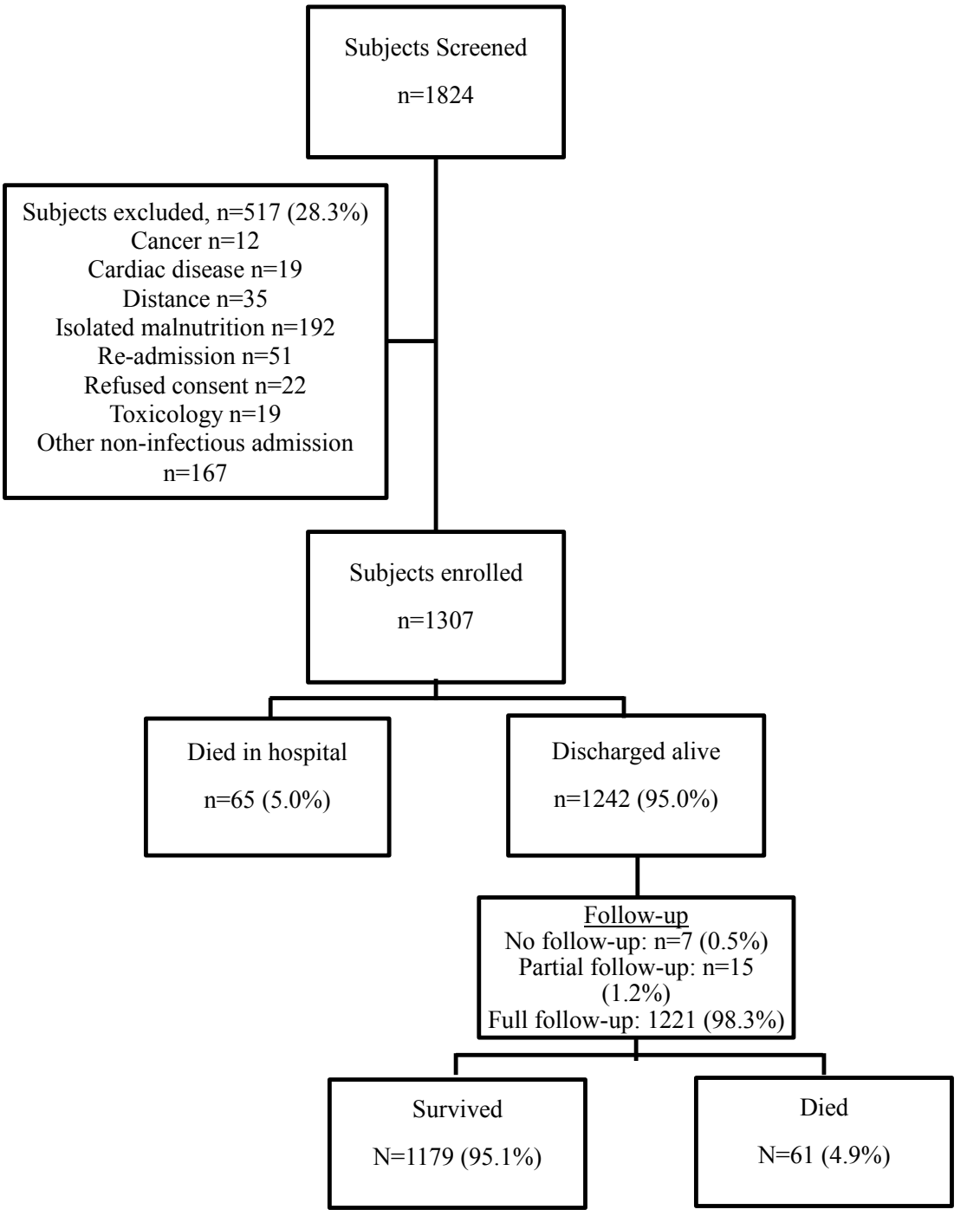

Figure 5.1. Consort diagram of study flow

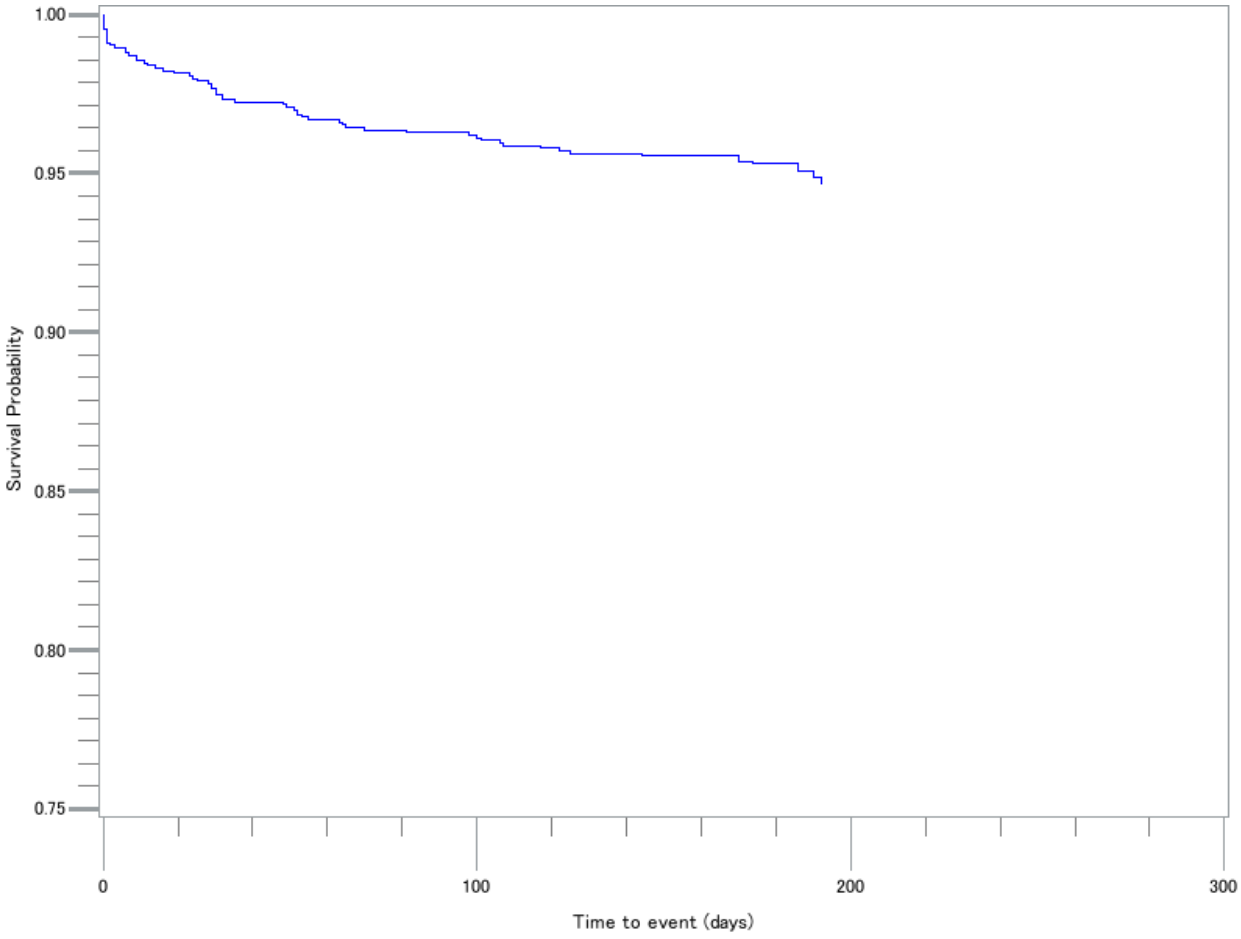

Figure 5.2. Kaplan-Meier curve of mortality after discharge

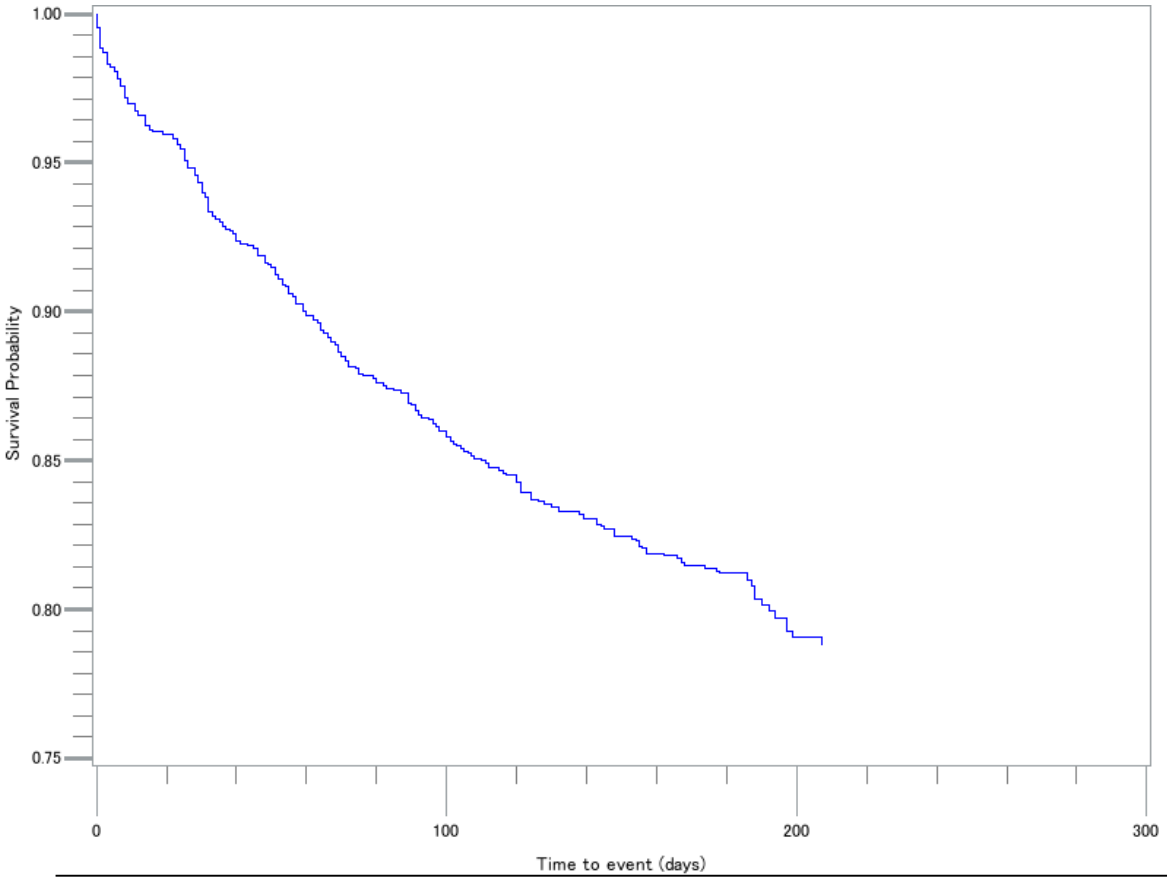

Figure 5.3. Kaplan-Meier curve of composite of mortality or readmission after discharge

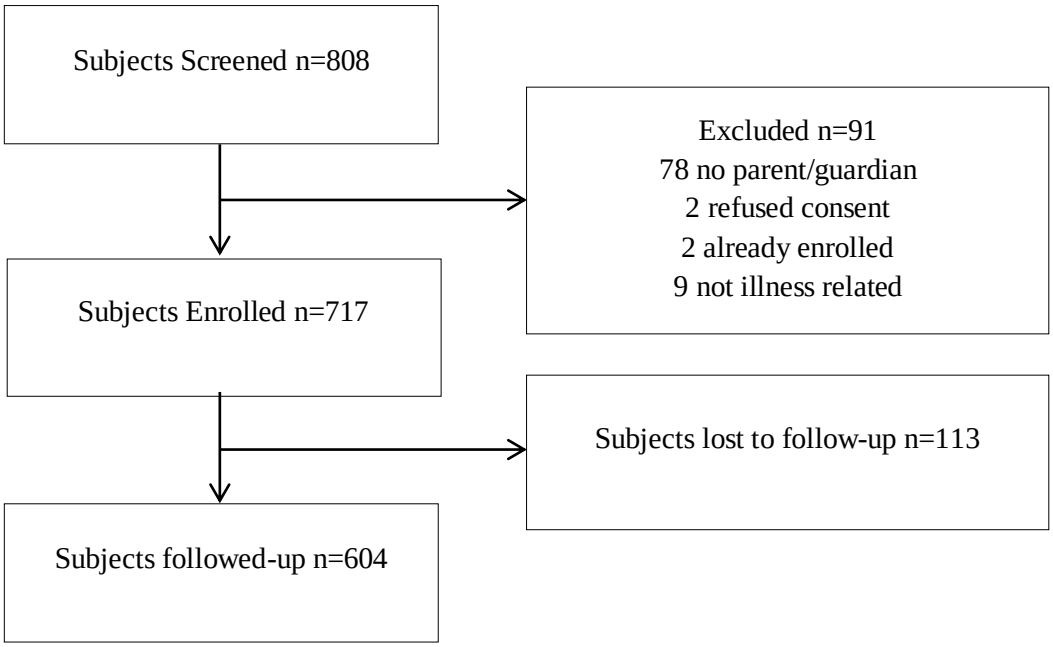

Figure 7.1 Consort diagram of study flow

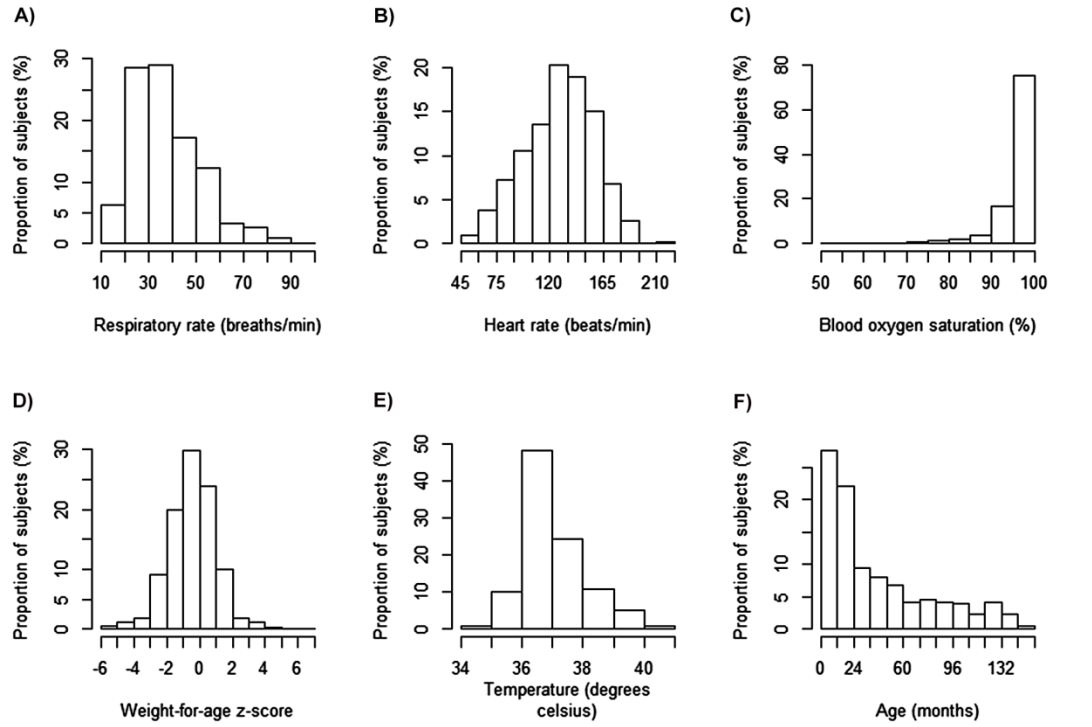

Figure 7.2 Distributions of select baseline clinical variables

Figure 8.1. Consort diagram of study flow

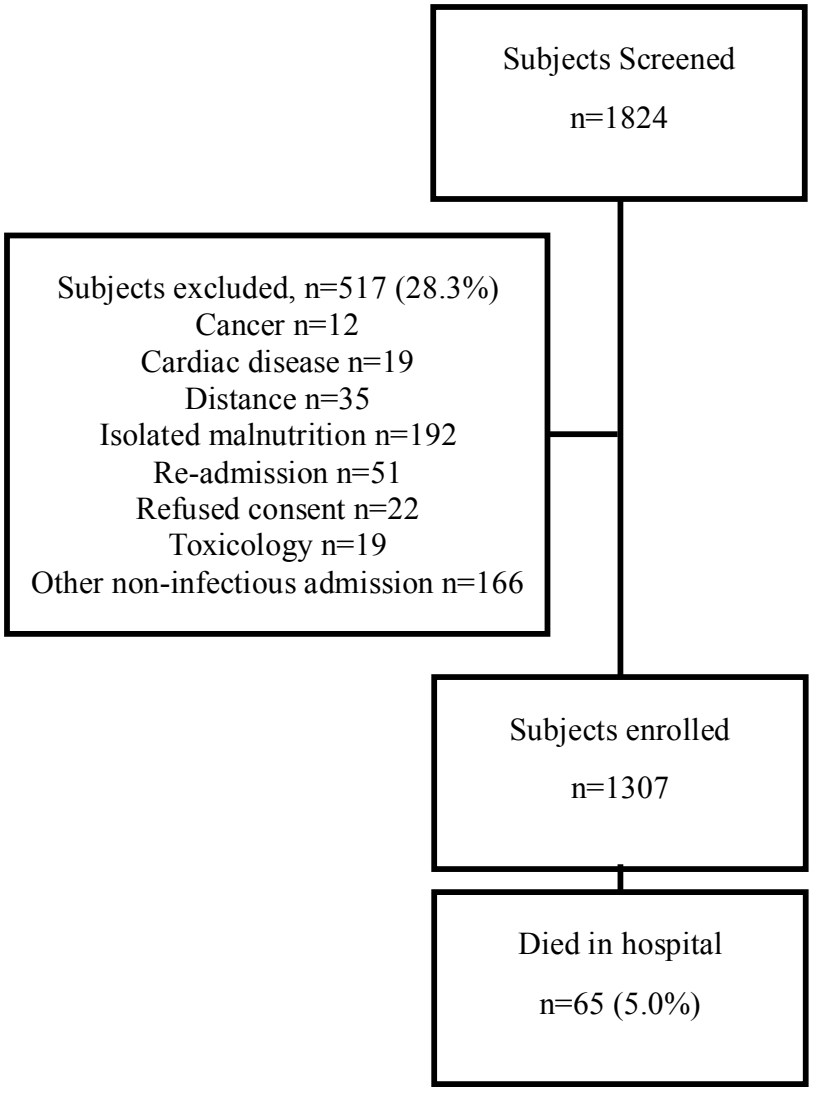

Figure 9.1. Consort diagram of study flow

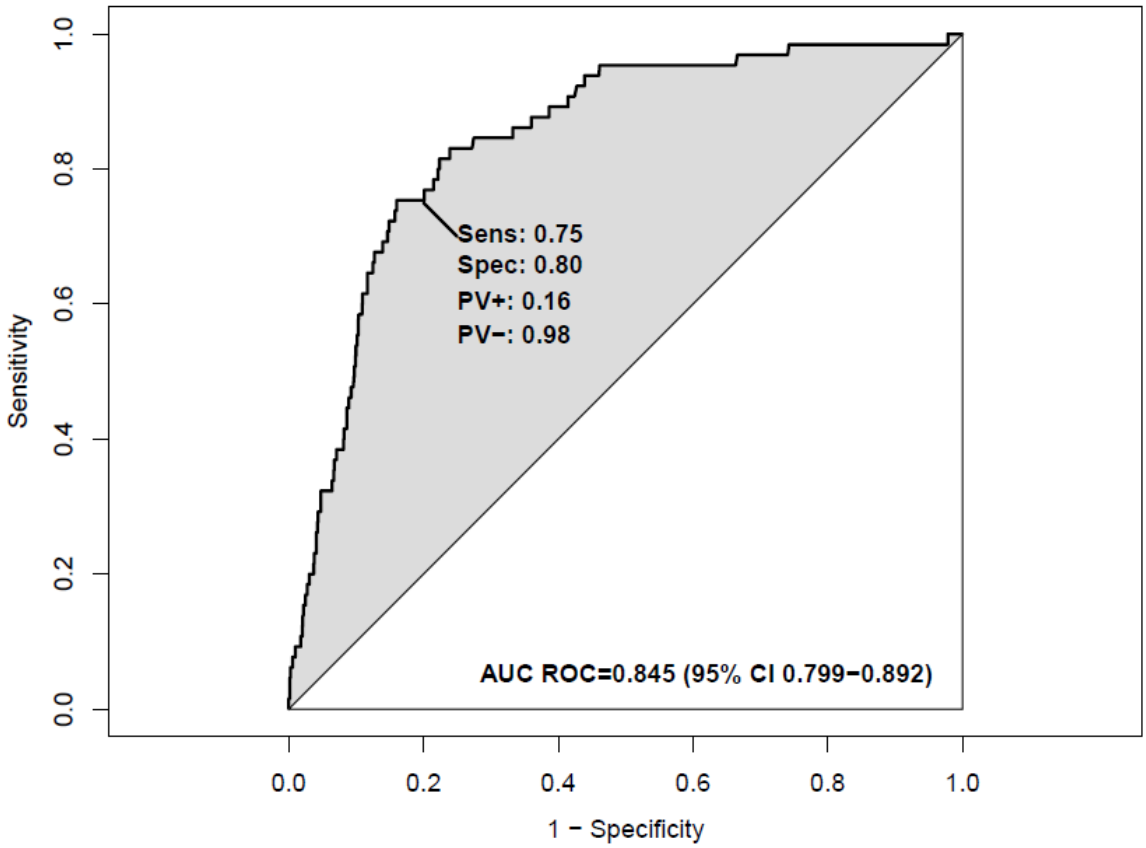

Figure 9.2. Primary model receiver operating curve characteristics
ROC = receiver operating characteristic; Sens = sensitivity; Spec = specificity;
PV - = negative predictive value; PV+ = positive predictive value

References

1. United Nations, General Assembly 56th session. *Road Map towards the Implementation of the United Nations Millennium Development Declaration: Report of the Secretary-General (UN Document No. A/56/326)*. New York; 2001.

2. *The Millennium Development Goals Report 2014*. New York: United Nations; 2014. http://mdgs.un.org/unsd/mdg/Resources/Static/Products/Progress2014/English2014.pdf.

3. Wang H, Liddell C a, Coates MM, 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*. 2014:957-979. doi:10.1016/S0140-6736(14)60497-9.

4. You D, Hug L, Chen Y, Wardlaw T, Newby H. *Levels and Trends in Child Mortality: Report 2014*. New York: United Nations Children's Fund; 2014. http://www.childmortality.org/files_v17/download/unicef-2013-child-mortality-report-LR-10_31_14_195.pdf.

5. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379(9832):2151-2161. doi:10.1016/S0140-6736(12)60560-1.

6. Murray CJL, Rosenfeld LC, Lim SS, et al. Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet*. 2012;379(9814):413-431. doi:10.1016/S0140-6736(12)60034-8.

7. Nair H, Simões E a F, Rudan I, 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;381(9875):1380-1390. doi:10.1016/S0140-6736(12)61901-1.

8. Izadnegahdar R, Cohen AL, Klugman KP, Qazi S a. Childhood pneumonia in developing countries. *Lancet Respir Med*. 2013;1(7):574-584. doi:10.1016/S2213-2600(13)70075-4.

9. Walker CLF, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet*. 2013;381(9875):1405-1416. doi:10.1016/S0140-6736(13)60222-6.

10. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*. 2013;382(9890):427-451. doi:10.1016/S0140-6736(13)60937-X.

11. Olofin I, McDonald CM, Ezzati M, et al. Associations of suboptimal growth with all-cause and cause-specific mortality in children under five years: a pooled analysis of ten prospective studies. *PLoS One*. 2013;8(5):e64636. doi:10.1371/journal.pone.0064636.

12. 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.

13. Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. *Am J Trop Med Hyg*. 2012;86(5):756-763. doi:10.4269/ajtmh.2012.11-0743.

14. Korpe PS, Petri WA. Environmental enteropathy: Critical implications of a poorly understood condition. *Trends Mol Med*. 2012;18(6):328-336. doi:10.1016/j.molmed.2012.04.007.Environmental.

15. Bhutta Z a, Ahmed T, Black RE, et al. What works? Interventions for maternal and child undernutrition and survival. *Lancet*. 2008;371(9610):417-440. doi:10.1016/S0140-6736(07)61693-6.

16. Kau AL, Ahern PP, Griffin NW, Goodman AL, Jeffrey I. Human nutrition, the gut microbiome, and immune system: Envisioning the future. *Nature*. 2012;474(7351):327-336. doi:10.1038/nature10213.Human.

17. Zucker JR, Lackritz EM, Ruebush TK, et al. Childhood mortality during and after hospitalization in western Kenya: effect of malaria treatment regimens. *Am J Trop Med Hyg*. 1996;55(6):655-660. http://www.ajtmh.org/cgi/content/abstract/55/6/655. Accessed January 27, 2011.

18. Berkley JA, Lowe BS, Mwangi I, et al. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med*. 2005;352(1):39-47. doi:10.1056/NEJMoa040275.

19. Moïsi JC, Gatakaa H, Berkley JA, et al. Excess child mortality after discharge from hospital in Kilifi, Kenya: a retrospective cohort analysis. *Bull World Health Organ*. 2011;89(10):725-732. doi:10.2471/BLT.11.089235.

20. Veirum JE, Sodeman M, Biai S, Hedegård K, Aaby P. Increased mortality in the year following discharge from a paediatric ward in Bissau, Guinea-Bissau. *Acta Paediatr*. 2007;96(12):1832-1838. doi:10.1111/j.1651-2227.2007.00562.x.

21. Villamor E, Misegades L, Fataki MR, Mbise RL, Fawzi WW. Child mortality in relation to HIV infection, nutritional status, and socio-economic background. *Int J Epidemiol*. 2005;34(1):61-68. doi:10.1093/ije/dyh378.

22. Biai S, Rodrigues A, Gomes M, et al. Reduced in-hospital mortality after improved management of children under 5 years admitted to hospital with malaria: randomised trial. *Br Med J*. 2007;335(7625):862. doi:10.1136/bmj.39345.467813.80.

23. Phiri KS, Calis JCJ, Faragher B, et al. Long term outcome of severe anaemia in Malawian children. *PLoS One*. 2008;3(8):e2903. doi:10.1371/journal.pone.0002903.

24. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8. doi:10.1097/01.PCC.0000149131.72248.E6.

25. Shah S, Bachur R, Kim D, Neuman MI. Lack of predictive value of tachypnea in the diagnosis of pneumonia in children. *Pediatr Infect Dis J*. 2010;29(5):406-409. doi:10.1097/INF.0b013e3181cb45a7.

26. Berkley JA, Maitland K, Mwangi I, et al. Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study. *BMJ*. 2005;330(7498):995. doi:10.1136/bmj.38408.471991.8F.

27. Bone R, Balk R, Cerra F, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644. http://chestjournal.chestpubs.org/content/101/6/1644.abstract. Accessed January 28, 2011.

28. Brilli RJ, Goldstein B. Pediatric sepsis definitions: past, present, and future. *Pediatr Crit Care Med*. 2005;6(3 Suppl):S6-S8. doi:10.1097/01.PCC.0000161585.48182.69.

29. Singhi S, Khilnani P, Lodha R, et al. Guidelines for treatment of septic shock in resource limited environments. *J Pediatr Infect Dis*. 2009;4(2):173-192. http://iospress.metapress.com/index/W4134546448L347X.pdf. Accessed January 28, 2011.

30. Carcillo JA, Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med*. 2002;30(2):1365-1378. http://www.scielo.br/scielo.php?pid=S0021-75572002000600004&script=sci_arttext&tlng=en. Accessed January 28, 2011.

31. Wang Y, Sun B, Yue H, et al. An epidemiologic survey of pediatric sepsis in regional hospitals in China. *Pediatr Crit care Med*. 2014;15(9):814-820. doi:10.1097/PCC.0000000000000247.

32. Kissoon N. Sepsis in children: A dark cloud with a silver lining. *Pediatr Crit care Med*. 2014;15(9):899-901. doi:10.1097/PCC.0000000000000264.

33. Phiri K, Esan M, van Hensbroek MB, et al. Intermittent preventive therapy for malaria with monthly artemether-lumefantrine for the post-discharge management of severe anaemia in children aged 4-59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial. *Lancet Infect Dis*. 2012;12(3):191-200. doi:10.1016/S1473-3099(11)70320-6.

34. 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;77(2):144-148. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2557604&tool=pmcentrez&rendertype=abstract.

35. *Uganda Health System Assessment 2011*. Kampala, Uganda and Bethesda, MD: Abt Associates Inc. http://www.healthsystems2020.org/content/resource/detail/85897/. Accessed December 30, 2014.

36. Watson RS, Carcillo J. Scope and epidemiology of pediatric sepsis. *Pediatr Crit Care Med*. 2005;6(3 Suppl):S3-S5. doi:10.1097/01.PCC.0000161289.22464.C3.

37. Most U.S. Adults Unfamiliar with Sepsis, One of Nation's Leading Causes of Death. 2010. http://www.feinsteininstitute.org/2010/09/most-u-s-adults-unfamiliar-with-sepsis-one-of-nations-leading-causes-of-death/.

38. Rubulotta FM, Ramsay G, Parker MM, Dellinger RP, Levy MM, Poeze M. An international survey: Public awareness and perception of sepsis. *Crit Care Med*. 2009;37(1):167-170. http://www.ncbi.nlm.nih.gov/pubmed/19050638.

39. Health topics. The pages linked to below contain links to WHO projects, initiatives, activities, information products, and contacts, organized by health and development topics. 2014. http://www.who.int/topics/en/. Accessed March 1, 2015.

40. Subhi R, Adamson M, Campbell H, Weber M, Smith K, Duke T. The prevalence of hypoxaemia among ill children in developing countries: a systematic review. *Lancet Infect Dis*. 2009;9(4):219-227. doi:10.1016/S1473-3099(09)70071-4.

41. World Health Organization. *Integrated Management of Childhood Illness: Distance Learning Course*. Geneva: World Health Organization; 2014.

42. Ashraf H, Alam NH, Chisti MJ, Salam MA, Ahmed T, Gyr N. Observational follow-up study following two cohorts of children with severe pneumonia after discharge from day care clinic/hospital in Dhaka, Bangladesh. *BMJ Open*. 2012;2(4). doi:10.1136/bmjopen-2012-000961.

43. Wiens MO, Kumbakumba E, Kissoon N, Ansermino JM, Ndamira A, Larson CP. Pediatric sepsis in the developing world: challenges in defining sepsis and issues in post-discharge mortality. *Clin Epidemiol*. 2012;4:319-325. doi:10.2147/CLEP.S35693.

44. Stroup DF. Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting. *J Am Med Assoc*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008.

45. Klugman J. *Human Development Report 2011*. New York: United Nations Development Program; 2011. http://hdr.undp.org/en/media/HDR_2011_EN_Complete.pdf.

46. 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;42(6):342-347. http://www.ncbi.nlm.nih.gov/pubmed/9009560.

47. Hennart P, Beghin D, Bossuyt M. Long-term follow-up of severe protein-energy malnutrition in Eastern Zaïre. *J Trop Pediatr*. 1987;33(1):10-12. http://www.ncbi.nlm.nih.gov/pubmed/3106648.

48. Stanton B, Clemens J, Khair T, Shahid N. Follow-up of children discharged from hospital after treatment for diarrhoea in urban Bangladesh. *Trop Geogr Med*. 1986:113-118. http://ukpmc.ac.uk/abstract/MED/3738979. Accessed January 30, 2013.

49. Roy S, Chowdhury A, Rahaman M. Excess mortality among children discharged from hospital after treatment for diarrhoea in rural Bangladesh. *Br Med J*. 1983;287:1097-1099. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1549963&tool=pmcentrez&rendertype=abstract.

50. Krumholz HM. Post-Hospital Syndrome — An Acquired , Transient Condition. *N Engl J Med*. 2013;368(2):100-102. doi:10.1056/NEJMp1211581.

51. Mangia CMF, Kissoon N, Carcillo JA. Sepsis and septic shock: A global overview. *J Pediatr Infect Dis*. 2009;4(2):71-76. http://iospress.metapress.com/index/K0675874488027W0.pdf. Accessed January 27, 2011.

52. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003;348(2):138-150. doi:10.1056/NEJMra021333.

53. World Health Organization. *Handbook IMCI: Integrated Management of Childhood Illness*. World Health Organization; 2006. http://books.google.com/books?hl=en&lr=&id=4Zhk4Y6UshcC&oi=fnd&pg=PR9&dq=Handbook:+IMCI+integrated+management+of+childhood+illness&ots=Ik9u40zA5O&sig=vgnON6F-7WFXos4n3emes18IKsg. Accessed December 30, 2014.

54. Baqui AH, El-arifeen S, Darmstadt GL, et al. Effect of community-based newborn-care intervention package implemented through two service-delivery strategies in Sylhet district, Bangladesh: a cluster-randomised controlled trial. *Lancet*. 2008;371:1936-1944.

55. Liu L, Oza S, Hogan D, 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):430-440. doi:10.1016/S0140-6736(14)61698-6.

56. Wiens M, Pawluk S, Kissoon N. Pediatric Post-Discharge Mortality in Resource Poor Countries: A Systematic Review. *PLoS One*. 2013;8(6):e66698. doi:10.1371/journal.pone.0066698.

57. Royston P, Moons KGM, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. *Br Med J*. 2009;338:b604. doi:10.1136/bmj.b604.

58. Hemingway H, Riley RD, Altman DG. Ten steps towards improving prognosis research. *Br Med J*. 2009;339:b4184. doi:10.1136/bmj.b4184.

59. Hsu C, Ohio T. The Delphi technique: Making sense of consensus. *Pract Assessment, Res Eval*. 2007;12(10):1-8. http://pareonline.net/getvn.asp?v=12&n=10.

60. Von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet*. 2011;377(9761):219-227. doi:10.1016/S0140-6736(10)61351-7.

61. Molyneux E, Mathanga D, Witte D, Molyneux M. Practical issues in relation to clinical trials in children in low-income countries: experience from the front line. *Arch Dis Child*. 2012;97:848-851. doi:10.1136/archdischild-2011-301476.

62. Karlen W, Dumont G, Petersen C, 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. In: *Proceedings of the International Conference on Health Informatics*. Rome, Italy: SciTePress; 2011:433-438.

63. The WHO Child Growth Standards. 2006. http://www.who.int/childgrowth/standards/en/. Accessed March 1, 2015.

64. Fleming S, Thompson M, Stevens R, 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):1011-1018.

65. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555-576.

66. 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):377-381.

67. Wiens MO, Kissoon N, Kumbakumba E, et al. Selecting candidate predictor variables for the modelling of post-discharge mortality: A protocol development project. *Submitted*. 2015.

68. Hosmer DW, Lemeshow S. Goodness of fit tests for the multiple logistic regression model. *Commun Stat - Theory Methods*. 1980;9(10):1043-1069. http://www.tandfonline.com/doi/abs/10.1080/03610928008827941.

69. Van Buuren S, Groothuis-Oudshoorn K. Multivariate Imputation by Chained Equations. *J Stat Softw*. 2011;45(3):1-67. doi:10.1177/0962280206074463.

70. 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). doi:10.1371/journal.pone.0066030.

71. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet*. 2010;376(9755):1838-1845. doi:10.1016/S0140-6736(10)61997-6.

72. 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. doi:10.1007/s10995-015-1695-0.

73. 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*. 2013;13(1):95. doi:10.1186/1472-6947-13-95.

74. Molyneux E, Ahmad S, Robertson A. Improved triage and emergency care for children reduces inpatient mortality in a resource-constrained setting. *Bull World Health Organ*. 2006;84(04):314-319. doi:10.2471/BLT.04.019505.

75. Walker N, Yenokyan G, Friberg IK, Bryce J. Patterns in coverage of maternal, newborn, and child health interventions: projections of neonatal and under-5 mortality to 2035. *Lancet*. 2013;382(9897):1029-1038. doi:10.1016/S0140-6736(13)61748-1.

76. SAS Institute Inc. *SAS/STAT 9.2 User's Guide*. Carey, NC: SAS Institute; 2008. doi:10.1111/j.1532-5415.2004.52225.x.

77. Jolliffe IT. *Principal Component Analysis*. 2nd Editio. New York: Springer; 2002. doi:10.2307/1270093.

78. Bedford KJA, Sharkey AB. Local barriers and solutions to improve care-seeking for childhood pneumonia, diarrhoea and malaria in Kenya, Nigeria and Niger: A qualitative study. *PLoS One*. 2014;9(6):1-15. doi:10.1371/journal.pone.0100038.

79. Adedini SA, Odimegwu C, Bamiwuye O, Fadeyibi O, De Wet N. Barriers to accessing health care in Nigeria: Implications for child survival. *Glob Health Action*. 2014;7:1-10. doi:10.3402/gha.v7.23499.

80. Kadobera D, Sartorius B, Masanja H, Mathew A, Waiswa P. The effect of distance to formal health facility on childhood mortality in rural Tanzania, 2005-2007. *Glob Health Action*. 2012;5:1-9. doi:10.3402/gha.v5i0.19099.

81. MacQueen KM, McLellan E, Kay K, Milstein B. Codebook Development for Team-Based Qualitative Analysis. *Cult Anthropol Methods*. 1998;10(2):31-36. doi:10.1177/1525822X980100020301.

82. Kayode GA, Adekanmbi VT, Uthman OA. Risk factors and a predictive model for under-five mortality in Nigeria: evidence from Nigeria demographic and health survey. *BMC Pregnancy Childbirth*. 2012;12(1):10. doi:10.1186/1471-2393-12-10.

83. Rutherford ME, Mulholland K, Hill PC. How access to health care relates to under-five mortality in sub-Saharan Africa: Systematic review. *Trop Med Int Heal*. 2010;15(5):508-519. doi:10.1111/j.1365-3156.2010.02497.x.

84. Rutherford ME, Dockerty JD, Jasseh M, et al. Access to health care and mortality of children under 5 years of age in the Gambia: a case-control study. *Bull World Health Organ*. 2009;87(January):216-224. doi:10.2471/BLT.08.052175.

85. Bazzano AN, Kirkwood BR, Tawiah-Agyemang C, Owusu-Agyei S, Adongo PB. Beyond symptom recognition: Care-seeking for ill newborns in rural Ghana. *Trop Med Int Heal*. 2008;13(1):123-128. doi:10.1111/j.1365-3156.2007.01981.x.

86. Noordam AC, Carvajal-Velez L, Sharkey AB, Young M, Cals JWL. Care Seeking Behaviour for Children with Suspected Pneumonia in Countries in Sub-Saharan Africa with High Pneumonia Mortality. *PLoS One*. 2015;10:e0117919. doi:10.1371/journal.pone.0117919.

87. Taffa N, Chepngeno G. Determinants of health care seeking for childhood illnesses in Nairobi slums. *Trop Med Int Heal*. 2005;10(3):240-245. doi:10.1111/j.1365-3156.2004.01381.x.

88. Hill Z, Kendall C, Arthur P, Kirkwood B, Adjei E. Recognizing childhood illnesses and their traditional explanations: Exploring options for care-seeking interventions in the context of the IMCI strategy in rural Ghana. *Trop Med Int Heal*. 2003;8(7):668-676. doi:10.1046/j.1365-3156.2003.01058.x.

89. Wilson SE, Ouédraogo CT, Prince L, et al. Caregiver recognition of childhood diarrhea, care seeking behaviors and home treatment practices in rural Burkina Faso: a cross-sectional survey. *PLoS One*. 2012;7(3):e33273. doi:10.1371/journal.pone.0033273.

90. Rutebemberwa E, Kallander K, Tomson G, Peterson S, Pariyo G. Determinants of delay in care-seeking for febrile children in eastern Uganda. *Trop Med Int Heal*. 2009;14(4):472-479. doi:10.1111/j.1365-3156.2009.02237.x.

91. Sonego M, Pellegrin MC, Becker G, Lazzerini M. Risk Factors for Mortality from Acute Lower Respiratory Infections (ALRI) in Children under Five Years of Age in Low and Middle-Income Countries: A Systematic Review and Meta-Analysis of Observational Studies. *PLoS One*. 2015;10:e0116380. doi:10.1371/journal.pone.0116380.

92. Singh R, Tripathi V. Under-five mortality among mothers employed in agriculture: findings from a nationally representative sample. *PeerJ*. 2015;3:e710. doi:10.7717/peerj.710.

93. Seguin M, Niño Zarazúa M. Non-clinical interventions for acute respiratory infections and diarrhoeal diseases among young children in developing countries. *Trop Med Int Heal*. 2015;20(2):146-169. doi:10.1111/tmi.12423.

94. Aiello AE, Larson EL. What is the evidence for a causal link between hygiene and infections? *Lancet Infect Dis*. 2002;2:103-110. doi:10.1016/S1473-3099(02)00184-6.

95. Lindblade K a, Hamel MJ, Feikin DR, et al. Mortality of sick children after outpatient treatment at first-level health facilities in rural western Kenya. *Trop Med Int Heal*. 2007;12(10):1258-1268. doi:10.1111/j.1365-3156.2007.01898.x.

96. Kissoon N. Out of Africa--a mother's journey. *Pediatr Crit Care Med*. 2011;12(1):73-79. doi:10.1097/PCC.0b013e3181ce74ef.

97. Modi P, Mark Munyaneza RB, Goldberg E, et al. Oxygen saturation can predict pediatric pneumonia in a resource-limited setting. *J Emerg Med*. 2013;45(5):752-760. doi:10.1016/j.jemermed.2013.04.041.

98. World Health Organization. *WHO/UNICEF Joint Statement: Integrated Community Case Management. An Equity-Focused Strategy to Improve Access to Essential Treatment Services for Children*. Geneva: World Health Organization; 2012.

99. *Uganda Clinical Guidelines 2010: National Guidelins on Management of Common Conditions*. Kampala, Uganda, Uganda; 2010. http://www.health.go.ug/docs/ucg_2010.pdf.

100. Hudson J, Nguku SM, Sleiman J, et al. Usability testing of a prototype Phone Oximeter with healthcare providers in high- and low-medical resource environments. *Anaesthesia*. 2012;67(9):957-967. doi:10.1111/j.1365-2044.2012.07196.x.

101. Karlen W, Kobayashi K, Ansermino JM, Dumont G a. Photoplethysmogram signal quality estimation using repeated Gaussian filters and cross-correlation. *Physiol Meas*. 2012;33(10):1617-1629. doi:10.1088/0967-3334/33/10/1617.

102. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15(4):361-387. doi:10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4.

103. Feikin DR, Nguyen LM, Adazu K, et al. The impact of distance of residence from a peripheral health facility on pediatric health utilisation in rural western Kenya. *Trop Med Int Health*. 2009;14(1):54-61. doi:10.1111/j.1365-3156.2008.02193.x.

104. Schoeps A, Gabrysch S, Niamba L, Sié A, Becher H. The effect of distance to health-care facilities on childhood mortality in rural Burkina Faso. *Am J Epidemiol*. 2011;173(5):492-498. doi:10.1093/aje/kwq386.

105. Siedner MJ, Lankowski A, Tsai AC, et al. GPS-measured distance to clinic, but not self-reported transportation factors, are associated with missed HIV clinic visits in rural Uganda. *AIDS*. 2013;27(9):1503-1508. doi:10.1097/QAD.0b013e32835fd873.

106. Corfield AR, Lees F, Zealley I, et al. Utility of a single early warning score in patients with sepsis in the emergency department. *Emerg Med J*. 2014;31(6):482-487. doi:10.1136/emermed-2012-202186.

107. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign. *Crit Care Med*. 2013;41(2):580-637. doi:10.1097/CCM.0b013e31827e83af.

108. Duke T. Systemic inflammatory response syndrome and bacteremia in developing countries. *Pediatr Crit Care Med*. 2010;11(1):153-154. doi:10.1097/PCC.0b013e3181b80e43.

109. *Uganda Clinical Guidelines 2010: National Guidelines on the Managment of Common Conditions*. Kampala, Uganda; 2010.

110. Pavare J, Grope I, Gardovska D. Prevalence of systemic inflammatory response syndrome(SIRS) in hospitalized children: a point prevalence study. *BMC Pediatr*. 2009;9(1):25. doi:10.1186/1471-2431-9-25.

111. Seiger N, Maconochie I, Oostenbrink R, Moll H a. Validity of different pediatric early warning scores in the emergency department. *Pediatrics*. 2013;132(4):e841-e850. doi:10.1542/peds.2012-3594.

112. Mackway-Jones K, Marsden J, Windle J, eds. *Emergency Triage*. 2nd ed. Oxford, UK: Blackwell Publishing; 2006.

113. Gilboy N, Paula T, Travers DA. The Emergency Severity Index Version 4: changes to ESI level 1 and pediatric fever criteria. *J Emerg Nurs*. 2005;31(4):357-362.

114. Warren DW, Jarvis A, LeBlanc L, Gravel J. Revisions to the Canadian Triage and Acuity Scale paediatric guidelines (PaedCTAS). *Can J Emerg Med*. 2008;10(3):224-243.

115. Clifton DC, Ramadhani HO, Msuya LJ, et al. Predicting mortality for paediatric inpatients where malaria is uncommon. *Arch Dis Child*. 2012;97(10):889-894. doi:10.1136/archdischild-2012-301812.Predicting.

116. Weiss SL, Parker B, Bullock ME, et al. Defining pediatric sepsis by different criteria. *Pediatr Crit Care Med*. 2012;13(4):e219-e226. doi:10.1097/PCC.0b013e31823c98da.

117. Pollack M, Ruttimann U, Getson P. Pediatric risk of mortality (PRISM) score. *Crit Care Med*. 1988;16(11):1110-1116. http://journals.lww.com/ccmjournal/Abstract/1988/11000/Pediatric_risk_of_mortality__PRISM__score.6.aspx. Accessed February 20, 2015.

118. Shann F, Pearson G, Slater a., Wilkinson K. Paediatric index of mortality (PIM): a mortality prediction model for children in intensive care. *Intensive Care Med*. 1997;23(2):201-207. doi:10.1007/s001340050317.

119. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med*. 2003;29(2):278-285. doi:10.1007/s00134-002-1601-2.

120. Emukule GO, McMorrow M, Ulloa C, et al. Predicting mortality among hospitalized children with respiratory illness in Western Kenya, 2009-2012. *PLoS One*. 2014;9(3):e92968. doi:10.1371/journal.pone.0092968.

121. Benatar S, Hewlett A, Nunn J. The use of iso-shunt lines for control of oxygen therapy. *Br J Anesth*. 1973;45(7):711-718. http://bja.oxfordjournals.org/content/45/7/711.short. Accessed February 20, 2015.

122. Kushniruk AW, Triola MM, Borycki EM, Stein B, Kannry JL. Technology induced error and usability: the relationship between usability problems and prescription errors when using a handheld application. *Int J Med Inform*. 2005;74(7-8):519-526. doi:10.1016/j.ijmedinf.2005.01.003.

123. Lewis JR. IBM Computer Usability Satisfaction Questionnaires: Psychometric Evaluation and Instructions for Use. *Int J Hum Comput Interact*. 1995;7(1):57-78. doi:10.1080/10447319509526110.

124. English M, English R, English a. Millennium Development Goals progress: a perspective from sub-Saharan Africa. *Arch Dis Child*. 2015;100(Suppl 1):S57-S58. doi:10.1136/archdischild-2013-305747.

125. Leon N, Sanders D, Damme W Van, et al. The role of "hidden" community volunteers in community-based health service delivery platforms: examples from sub-Saharan Africa. *Glob Health Action*. 2015;8(27214). doi:10.3402/gha.v8.27214.