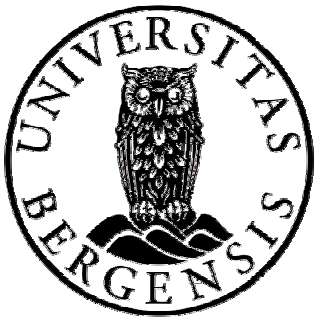
The challenge of improving the management of hospitalised children with severe acute malnutrition in Uganda

Hanifa Bachou



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Dedication

In memory of my beloved husband Dr Salim Ahmad Bachou (RIP) and all the severely malnourished children who lost their lives from preventable cause. May your souls rest in peace and may your deaths lead to a lasting solution to saving the lives of those who are yet to become malnourished.

Contributors

This thesis is the result of *Essential Nutrition and Child Health in Uganda*, a NUFU-funded collaborative project between the Department of Paediatrics & Child Health, Makerere Medical School, Makerere University, Kampala, Uganda and the Centre for International Health, University of Bergen, Norway.

The Department of Paediatrics and Child Health (DPCH), Makerere Medical School, Makerere University

DPCH employed the candidate and provided supervision through Professor James K Tumwine.

The Centre for International Health (CIH), University of Bergen

CIH provided the main supervision of the candidate through Professor Thorkild Tylleskär.

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Acronyms and definitions of terms

ACU	Acute Care Unit
AIDS	Acquired Immunodeficiency Syndrome
CI	Confidence interval
CMF	Case management form
CTC	Community-based Therapeutic Care
CQI	Continuous Quality Improvement
CQM	Continuous Quality Management
CXR	Chest X-ray
ELISA	Enzyme-linked Immunosorbent Assay
ETAT	Emergency Triage Assessment and Treatment
Hb	Haemoglobin
HR	Hazards Ratio
HIV	Human Immune deficiency Virus
MNU	Mwanamugimu Nutrition Unit
NCHS	National Center for Health Statistics
NGT	Nasogastric tube
OR	Odds Ratio
PI	Performance Improvement
QA	Quality Assurance
QI	Quality Improvement
ReSoMal	Rehydration Solution for Malnourished children
RUTF	Ready to use Therapeutic Food
SAM	Severe acute malnutrition
TQM	Total Quality Management
W/A	Weight for Age
WBC	White Blood cells
W/H	Weight-for-Height
WHO	World Health Organization
z-score	Standard deviation score

Study definitions

Severe acute malnutrition: A weight for height below -3 standard deviations and/or presence of bilateral pedal pitting oedema. The child's weight is expressed in standard deviations below the median weight of the NCHS/WHO reference population of children of the same height.

Oedema: Bilateral pitting oedema (=swelling) involving at least the feet: presence of such oedema means that the child has oedematous severe acute malnutrition (kwashiorkor or marasmic kwashiorkor).

Quality health care: Criteria that must be met by the inputs, process and outcomes standards of the healthcare delivery system in order to ensure optimum health gains for its population.

Performance improvement: A process for achieving the desired institutional and individual results.

Self-discharged patients: Patients who leave the hospital premises without informing the staff or who leave the hospital against medical advice.

List of papers

The thesis is based on the following four papers; they will be referred to in the text by Romans numerals:

I Hanifa Bachou, James K Tumwine, Robert KN Mwadime, Thorkild Tylleskär. Risk factors in hospital deaths in severely malnourished children in Kampala, Uganda. *BMC Pediatrics* 2006, **6**:7.

II Hanifa Bachou, James K Tumwine, Robert KN Mwadime, Ahmad Tahmeed, Thorkild Tylleskär. Reduction of unnecessary transfusion and intravenous fluids in severely malnourished children is not enough to reduce mortality. *Annals of Tropical Paediatrics (2008) 28, 23-33.*

III Hanifa Bachou, Thorkild Tylleskär, Robert Downing, James K Tumwine. Severe malnutrition with and without HIV-1 infection in hospitalised children in Kampala, Uganda: differences in clinical features, haematological findings and CD4+ cell counts. *BMC Infectious Diseases* 2006, 6:160

IV Hanifa Bachou, Thorkild Tylleskär, Herbert D Kaddu-Mulindwa, James K Tumwine. Bacteraemia among severely malnourished children infected and uninfected with the human immunodeficiency virus-1 in Kampala, Uganda. *Nutrition Journal* 2006, **5**:27

The list of errata is in appendix vi, page 77

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Support from my family
My beloved husband, Dr Salim Bachou (RIP): the four years was a nightmare for you with added responsibilities and having a 'mobile' wife. Thank you for being there for me and encouraging my academic pursuit up to the last moment of your life.
My beloved children, Junior Bakary, Jamal and Najmah, thank you for your sacrifice and continuous support and acceptance of a 'telephone mother'. My dad Hassan Mitchel, you are such a treasure to me, you comforted and prayed for my success. Thank you for the Sunday calls.

Summary

Millennium Development Goal (MDG) number 4 is to reduce the global mortality rate among under-fives by two thirds between 1990 and 2015. Efforts to prevent child deaths need to be stepped up in order to meet this target. World-wide, hospital case fatalities of severe acute malnutrition remain high.

Objectives: This study was designed to establish key factors contributing to the high case fatality rate among children with severe acute malnutrition admitted to Mulago Hospital, Uganda, to improve on these factors and to document the effect on case fatality.

Methods: A 'before' and 'after' design was used. A total of 450 children below the age of 60 months, with weight for height below -3 z-scores of the median NCHS reference or with oedema, were consecutively enrolled between September and December in 2003 and 2004 (220 pre- and 230 post-period, respectively). In both periods, we collected the following on admission to the hospital: socio-demographic data; blood for biochemical, haematological, blood culture and sensitivity and HIV-1 serology (ELISA/PCR) tests; urine for microscopy, culture and sensitivity; and a chest X-ray of each child enrolled. The child was then followed until discharge or death. We analysed the data, identified factors significantly associated with mortality and launched an improved practice.

Results: The results in the pre-period indicated that deaths within the first week of admission were significantly associated with inappropriate use of blood transfusions and IV fluids in the management of severe acute malnutrition. Promoting the appropriate use of blood transfusion and fluids in accordance with WHO recommendations resulted in: first, a significant reduction in inappropriate use of blood transfusions and IV infusions; second, a significant reduction in deaths associated with blood transfusion or IV fluid infusion during the first week from 82% (31/38) to 23% (8/35); third, a reduction of mortality during the first week from 70% to 61%. However, the overall case fatality rate was not reduced (24%, 24.8%). We also found that the children in the post period were more ill than those in the pre-period. The common co-morbidities were HIV infection, blood stream infections (septicaemia), diarrhoea and respiratory tract infections. These were more frequent in the post-period than in the pre-period, though we found no significant association with mortality.

Conclusions: These studies have shown that in Mulago Hospital, inappropriate management - outside that recommended for management of severe acute malnutrition - contributes to mortality. Partial implementation of WHO-recommended standardised care, as in this study, did not improve the overall case fatality rate. A holistic health system approach linked to improved resource allocation for paediatric clinical care is imperative in order to attain Millennium Development Goal number 4.

1. Introduction

Millennium Development Goal (MDG) number 4 is to reduce the mortality rates among under-fives by two thirds between 1990 and 2015 (1). A recent assessment showed that efforts to prevent child deaths need to be stepped up in order to meet that target (2). One of the most pressing questions in the field of nutrition and child health is how to reduce morbidity and mortality among children with severe acute malnutrition (3, 4). Undernutrition is a major contributory factor in over half the deaths and the high morbidity rate among children in low-income countries (5-11). It is perturbing to note that in sub-Saharan Africa, the nutritional and health situation is worsening (1, 12-15). Likewise, hospital case fatality rates for severe acute malnutrition remain high (1, 2, 16, 17). Poor quality of care, especially faulty case management, has been reported as the main cause of this high case fatality rate in resource-poor settings (18).

In Mulago Hospital, the national referral and teaching hospital situated in Kampala, the capital of Uganda, the prevalence of severe acute malnutrition among the under-fives admitted during 2003 was 10% with a case fatality rate of 24%. The annual admissions of children with severe acute malnutrition had increased considerably from less than 500 in 1995 to over 1000 in 2003 (figure 1); the case fatality rate had almost doubled (from 15% to 24%) and so had the length of hospital stay. This raised concern at the departmental and hospital level and generated the need to identify causes and possible solutions to the problem. The present study is a result of that concern.

1.1 Hospitalised children with severe acute malnutrition. Why are they dying?

Undernutrition is associated with high morbidity and > 50% of all childhood mortality in resource-poor settings (5, 7). The risk of dying from any cause increases 8 times in a child with severe underweight (11). Because of this high risk of death, many children with severe acute malnutrition are managed in hospitals. Unfortunately, many of them die anyway. The alterations in their physiological and metabolic functions predispose them

to complications including hypoglycaemia, hypothermia, electrolyte imbalance, heart failure and infections. If the condition is not diagnosed and treated promptly and appropriately, death is imminent, and the case fatality rate is over 50% in some hospitals (3, 19). The underlying factors are many and some are beyond the control of the health practitioners who, unfortunately, often bear most of the blame.

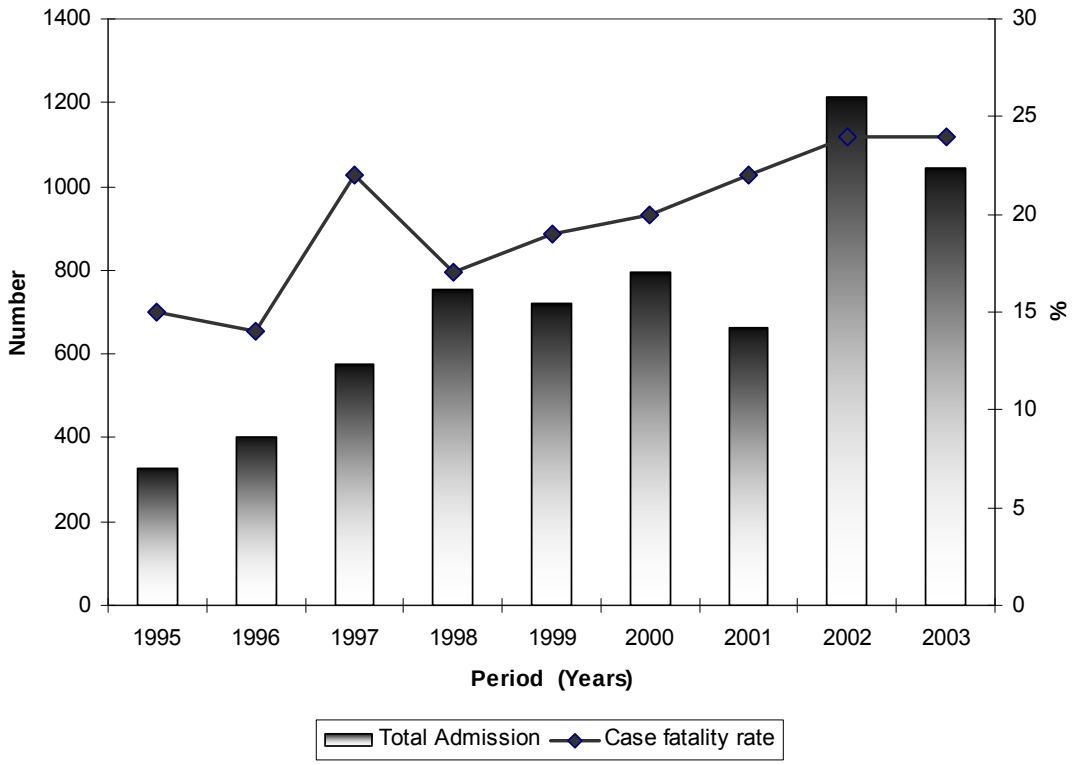

Figure 1. Number of annual admissions of children with severe acute malnutrition to Mulago Hospital (20) (bars, Y-axis to the left) and case fatality rates (line-points, Y-axis to the right).

The use of WHO guidelines on the management of severe acute malnutrition (21, 22) has led to successful treatment and reduction in mortality from this condition in both emergency (23) and hospital (24, 25) settings. The guidelines were based on long term clinical experience from various countries including Uganda (26) supported by pathophysiological reasoning (27, 28). They focus on ten general principles of management targeted at controlling or recognizing and treating the complications of

severe acute malnutrition. A recent review of over 140 studies agrees that the protocolised management would improve case fatality rates in children with this condition (18) .

Table 1. An overview of the general principles for management of children with severe acute malnutrition according to WHO (22).

	General principles for routine care 'The 10 essential steps'
1.	Treat/prevent hypoglycaemia
2.	Treat/prevent hypothermia
3.	Treat/prevent dehydration
4.	Correct electrolyte imbalance
5.	Treat/prevent infection
6.	Correct micronutrient deficiencies
7.	Start cautious feeding
8.	Achieve catch-up growth
9.	Provide sensory stimulation and emotional support
10.	Prepare for follow-up after recovery

Despite this improved understanding of the clinical management of severe acute malnutrition, the case fatality rate among affected children admitted to most hospitals in sub-Saharan Africa has remained unacceptably high, between 20 and 50% (2, 3). This has raised concern about whether the WHO guidelines provide a feasible and realistic approach for Africa (29-31). Factors that have been found to hinder optimal implementation of the guidelines and achievement of low mortality include (a) co-morbidities and (b) malfunctioning, under-resourced and overloaded health systems (32-35).

This calls for greater efforts to identify factors that impair the management of children with severe acute malnutrition in sub-Saharan hospitals and ways of reducing the case fatality rates. Undiagnosed heart failure caused by metabolic changes, inappropriate use of fluids/blood transfusion or disequilibrium syndrome during recovery have been hypothesized as major causes of hospital deaths in oedematous children (36-38). These

conditions may all contribute to excess sodium, with fluid shifts in the intravascular compartments resulting in fluid overload. If heart failure is erroneously treated as pneumonia (because increased respiratory rate is a sign common to both), then mortality is bound to increase. This has led to a different approach to prevent excess administration of fluids and to diagnose fluid overload using a weight-monitoring algorithm (39-41). However, its effectiveness needs to be evaluated against the already over-burdened and meager human resources in many African hospitals. Documentation of inappropriate use of fluids in the management of severe acute malnutrition in sub-Saharan hospitals is essential.

The danger signs in the WHO guidelines have been found to be less sensitive and less specific in predicting up to 50% of the deaths that occur during the first 48 hours. So are these children dying of some other unidentified cause such that the current guideline recommendations cannot salvage them? Is there a need for research to identify more sensitive and more specific clinical signs in these children to avoid early deaths? The proposed specific triage system for early identification of the 'at highest risk of death' group of children with severe acute malnutrition needs to be considered (42). Integrating such triage with screening, and admitting only those who need inpatient care, would further improve the quality of hospital management of severe acute malnutrition and possibly reduce case fatalities (39).

Co-morbidities

Mechanisms of humoral and cellular immuno-suppression have been widely studied in the past (43-47), and more recently using modern technology (48, 49). Severe acute malnutrition affects all organs in the body including the immune system. It is now established that severe acute malnutrition can lead to an immunocompromised state involving both humoral and cellular immunity; this has been referred to as Nutritionally Acquired Immunodeficiency Syndrome (NAIDS). However, the extent and severity of the condition is not easily assessed. Immunological depletion predisposes these children to acute bacterial/viral infections and chronic infections such as tuberculosis,

necessitating adequate investigation and prompt management with appropriate antibiotics. For resource-poor settings, the option of empirical antibiotic coverage has been recommended (22). There have been few studies to determine whether the types of bacteria infecting children with severe acute malnutrition are changing over time, or if they are developing resistance to the antibiotics used, or whether such changes affect the survival of children with severe acute malnutrition.

HIV infection has also been documented as common in children with severe acute malnutrition. Co-morbidity of NAIDS, HIV-I infection (AIDS) and TB has raised great concern (50). Deterioration of immunity against HIV and TB has increased the prevalence of these infections and the associated mortality among children in sub-Saharan Africa (14, 33, 51) and has also been associated with increased case fatality rates among children with severe acute malnutrition (33, 50, 52). Hence, the coexistence of HIV and TB in children with severe acute malnutrition could expedite deterioration and death. However, there is little information about the extent of immunological alteration caused by co-existence of the double immunological burden (NAIDS and AIDS) in these children. There is a need to document the contribution of HIV to the high case fatality rate of children with severe acute malnutrition in African health facilities, including those with adequate intensive services (34, 42).

There is still a lack of knowledge about the optimal care of a child infected with HIV/AIDS and with severe acute malnutrition. There is little information about the added immunological suppression in these children. An expert review of the WHO guidelines relating to ARV and prophylaxis against opportunistic secondary infections is in line with the national guideline for ARV therapy in children with confirmed HIV positive status and known $CD4^+$ lymphocyte count. However, the management guidelines for children with severe acute malnutrition have so far remained unaltered (40) (table 1).

The Sphere Project has tried to determine a minimum standard for relief operations (53). They also propose minimum standards for care of children with severe acute

malnutrition. These minimum standards could also be considered in hospital care of non-displaced populations (table 2).

Table 2. Key indicators for the management of children with severe acute malnutrition (53).

Characteristics	Minimum standards
A. Proportion of exits who have died	< 10%
B. Proportion exits recovered	> 75% (*cases of TB and HIV need to be documented & considered for long term treatment and care*)
C. Proportion self-discharged	< 15%
D. Mean weight gain per day	> 8g / Kg/ person/ day: (*may mask situations where children are not improving and are not being discharged*)
E. Medical care provided	According to proven clinical care protocols
F. Discharge criteria	Anthropometric indices, good appetite, no diarrhoea, no untreated illness, no micronutrient deficiency
G. Nutrition worker to patient ratio	1:10
H. All carers	Able to feed and care for these children
I. Time needed to attain above indicators	1-2 months

1.2 Quality improvement in health care

Quality improvement (QI) involves identifying unnecessary, redundant or incorrect parts of processes and making changes. However, because changing a process may not necessarily improve it, any change must be tested and studied to determine whether it has actually done so. Quality improvement looks at two major components: what is done (content) and how it is done (process of care). Either component could lead to improvement; however, it is more effective to address both components together.

Quality improvement projects are increasingly used in health institutions to effect measurable improvements in quality of care. Many of these projects have reported success. Substantial efforts have been dedicated to developing norms, standards, protocols, guidelines and assessment tools, based on clinical evidence. This has led to improvement, even with minimal addition to existing human resources. For example, the use of triage, assessment and treatment (ETAT) guidelines by nurses to identify children

requiring high priority treatment has been successful in some countries with low resources. In Malawi, nurses were able to identify 85% of children needing admission to hospital (54). In Brazil, in settings where ETAT was introduced, nurses initiated treatment in appropriately 90% of cases (55). In Peru, health centres that embraced self-assessment with internal problem-solving had lower case fatality rates than non-participating health centres (56). In-patient management of severe acute malnutrition has also been improved substantially with a standardized protocol and limited additional resources (24, 25).

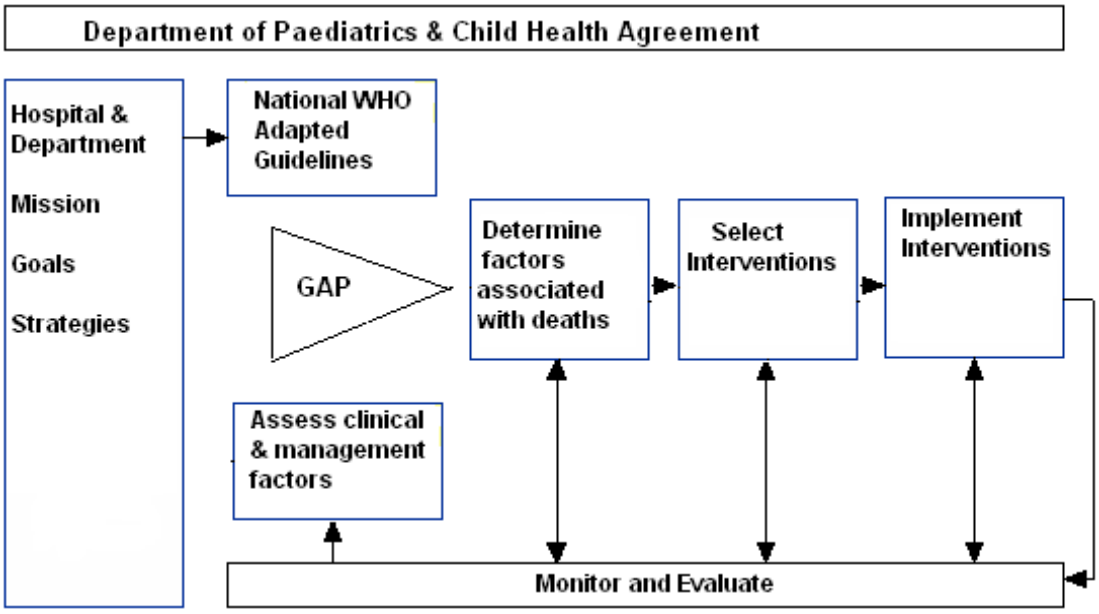

Figure 2. A modified performance improvement framework (57).

The quality of health care provided in any health institution plays a major role in patient outcome, regardless of the hospital setting. In some high-income countries, the incidence of errors in management of hospital patients, which often goes unnoticed, is reportedly close to 17% (58). While many of these errors are preventable, one fifth of them result in death or permanent disability. In many health institutions, children do not receive adequate ambulatory and/or institutional care. Surveys have revealed that many sick children are not properly assessed and treated (56, 59). Often severely ill children who require admission receive inadequate triage, assessment and treatment and, when

admitted, insufficient monitoring. This adversely affects the outcome of a significant proportion of hospitalised children, especially those with severe acute malnutrition, resulting in unnecessary suffering or avoidable death for many children each year.

Poor quality of care, especially faulty case management, has been reported as the main cause of the high case fatality rates from severe acute malnutrition in resource-poor settings (2, 16, 60). In order to reduce the hospital case fatality rate associated with severe acute malnutrition, UNICEF and WHO jointly agreed to develop and strengthen existing resources through training and development of treatment guidelines in low-resource settings (58), an effort targeted at improving the quality of health care in hospitals. A generic guideline for management of severe acute malnutrition was developed, applicable in both institutional and emergency settings; it was based on a set of ten principles with a minimum acceptable standard (21,22). This minimum standard set has been shown to be achievable in a hospital setting with minimal resources (16, 24, 35, 62, 63).

All aspects of quality of health care mentioned need be addressed in order to reduce case-fatality in resource-poor settings (57, 64, 65). However, to address all these aspects at the same time would require financial and manpower resources that are generally not available in such settings (66). The question is whether simple quality improvement interventions to reduce case fatalities would be sustainable in many hospitals in sub-Saharan Africa; as such intervention would include “behavioural changes” in service providers to match existing case-management guidelines. Also, the behaviours to be changed would need to have a proven impact on mortality.

The rationale for choosing this evidence-based approach (figure 2) was to promote ownership and sustainability of improved practice based on realistically available resources.

2. Aims of the thesis

The main aims of this thesis were (a) to establish risk factors for the high case fatality rate among children with severe acute malnutrition admitted to Mulago Hospital, (b) to involve the service providers in identifying factor(s) that can be improved within a short time with available resources, (c) collectively to implement the chosen practice and (d) to measure the effect of the improved practice.

Specific objectives

1. To establish the risk factors for excess deaths among hospitalised severely malnourished children below five years of age (Paper I).

2. To test whether standardising the use of blood transfusions and intravenous (IV) fluids could reduce fatalities among severely malnourished children admitted to Mulago Hospital, Kampala, Uganda (Paper II).

3. To describe the clinical features, haematological findings and $CD4^+$ and $CD8^+$ cell counts of severely malnourished children in relation to human immunodeficiency virus (HIV) infection (Paper III).

4. To establish the magnitude of bacteraemia in severely malnourished children, and to relate the types of bacteria and antimicrobial sensitivity to HIV status (Paper IV).

3. Subjects and methods

3.1 Study area

The studies in the current thesis were all conducted in the paediatric wards of the Mulago Hospital Complex, Department of Paediatrics and Child Health, Kampala, Uganda. The location and profile of Uganda are presented in figure 3 and table 3.

Figure 3. The location of Uganda and the study site in Central Kampala (Source: www.cdc.org and www.cia.gov/factbook/geos/ug.html)

An assessment of the burden of disease in Uganda in 1995 showed that 75% of the years of life lost through premature death were due to ten preventable diseases (67). Perinatal and maternal conditions accounted for 20%, malaria for 15.4%, acute lower respiratory tract infections 10.5%, AIDS 9.1% and diarrhoea 8.4%. Thirty-two percent of under-fives are stunted (below -2 z-score height-for-age), 25% are underweight and 5% wasted (68) (table 3).

Table 3. Uganda Facts and Figures (Source: United Nations Development Report, 2006) www.undp.or.ug/resources/45. Uganda Demographic Health Survey final report www.ubos.org *Statistical abstract 2002, www.health.go.ug

Indicator	Measure
Total population in 2006	27.4 million
Population growth rate	3.4 %
Proportion of the population below 15 years of age	50.8 %
Total fertility rate	6.7
Population density (/Km^2)	126
Infant mortality rate	81
Under-five mortality rate	152
Children < 5 years old stunted (height for age below -2SD)	38 %
Child wasting (weight for height below -2SD)	6 %
Child underweight (weight for age below -2 SD)	16%
Urban population	15.4 %
Adult illiteracy rate	68.9 %
GDP per capita (UShs) (2004-2005)	573,405
GDP growth rate	5.56 %
GDP per capita growth rate	2.2 %
Total number of health facilities*	1738
Hospitals*	104
Health facility physical accessibility*	49 %
Population / doctor	20,000
Population / nurse*	3,065
HIV prevalence	6.2 %

3.1.1 Mulago Hospital Complex

Mulago Hospital is the older of the two national referral and teaching hospitals in the country. The hospital was founded in 1913 by Sir Albert Cook as a small health centre for treating venereal diseases and sleeping sickness. It was later rebuilt into a modern teaching hospital and handed as an independence gift to the Republic of Uganda in October 1962. Owing to lack of proper maintenance, it was declared in a poor state by 1986. With funds from a number of international donor agencies including the World Bank and the International Atomic Energy Agency, most of the hospital structures were

rehabilitated. Currently the hospital has a bed capacity of 1500, an annual number of inpatient admissions of 120,000 and over 480,000 outpatient attendances. It provides general and specialised services including open-heart surgery. The situation at the hospital shows many constraints (69) as highlighted in table 4.

Table 4 Constraints in Mulago Hospital Complex

	Major Constraints	Implications
1	The decline in non-wage recurrent funds	Particularly for drugs, house rent, food for patients; causes serious operational problems. This item has so far fallen by Ug. Shs. 1.1 billion. This is further aggravated by inflation and depreciation of the Uganda shilling.
2	The shortage of staff	Shortage of over 300 staff affects the quality of care, particularly in nursing coverage. The Health Services Commission has now received submissions so that more staff can be recruited.
3	Increasing patient workload	It should therefore be appreciated that the lack of staff in the midst of declining resources puts extra strain on performance.
4	The absence of stores in the country	Absence of stores with a good stock of specialised items e.g. for intensive care, renal dialysis machines, laboratories, endoscopes and other specialised equipment prolongs the stock outs.

3.1.2 The Department of Paediatrics and Child Health

The Department of Paediatrics and Child Health is one of the busiest departments in the hospital offering inpatient and outpatient services to children and adolescents. It has a total of 5 general wards, one nutrition unit and an emergency unit called the Acute Care Unit (ACU). ACU acts as an admission ward and is the main entrance for all very sick children who come from the assessment centres, or are referred from other centres or self-referred. It is open 24 hours a day seven days a week and admits about 50-80 sick children daily. These patients are assessed every morning and subsequently admitted to one of the six wards. The Mwanamugimu Nutrition Unit (meaning a 'healthy child'

thrives on adequate breastfeeding), was started in 1965 for managing children with severe acute malnutrition and was at the time well known for research into the condition. The dilapidations of the 1970s did not exclude this unit. With a bed capacity of 65, it currently admits an average of 1100 children with severe acute malnutrition annually.

3.2 Study population and design

This study was constructed with a 'before and after' design. Between September and November 2003 and between September and December 2004, all the children below 60 months of age admitted to Mulago Hospital through the Acute Care Unit were screened for signs of severe acute malnutrition in accordance with WHO guidelines (22). Children who were found to have severe acute malnutrition were consecutively recruited into the study after obtaining written and signed consent from their caregivers. The time frame and study profile are shown in figures 4 and 5.

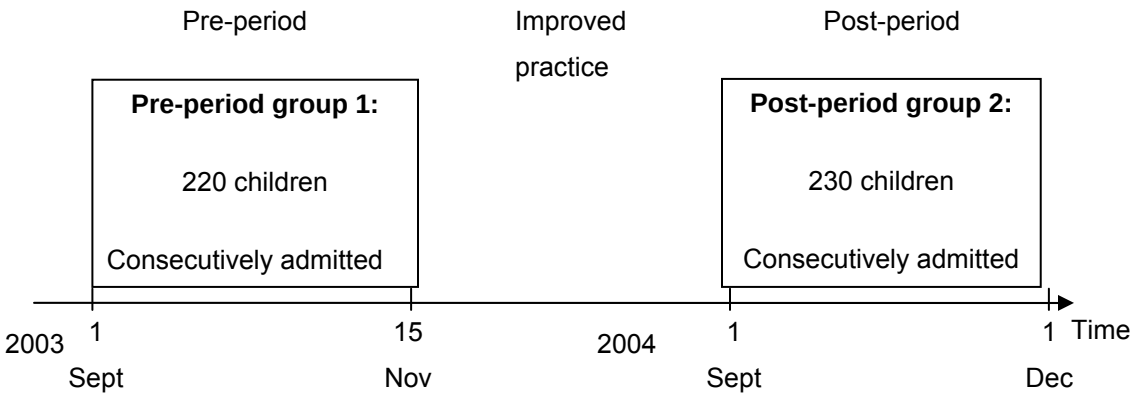

Figure 4. The time frame of the events in the study.

3.3 Enrolment and sample size

Routinely, all sick children admitted to Mulago Hospital are first triaged in the assessment center (ASC). Those found to be severely ill are sent to the ACU for management and overnight observation. Children who need further hospital care after the first night are admitted to one of the paediatric wards/units for further hospital management.

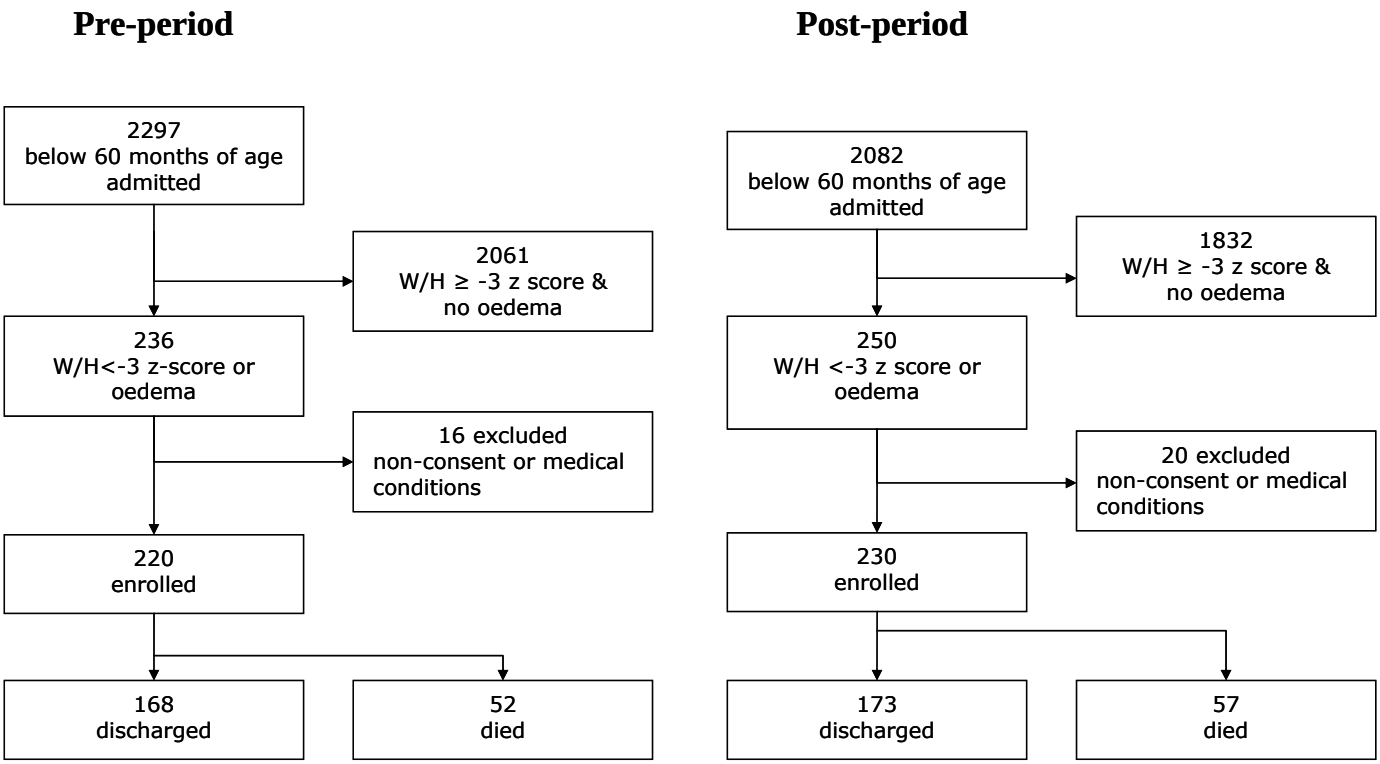

Figure 5. The study profile with the number of children screened, included and excluded, and the number of children at the different endpoints in the study.

All children below the age of 60 months admitted to the ACU for overnight observation during the study period were consecutively screened for severe acute malnutrition. They underwent physical examination including weight and height/length measurements. Those who met the WHO criteria for severe acute malnutrition and the study criteria were consecutively recruited into the study after obtaining written and signed consent from the caregivers. The respective caretaker provided a clinical history and subsequently blood and urine specimens were obtained from the child. The caregiver was then requested and assisted to take the child for a chest X-ray. These children were subsequently followed-up daily by experienced study doctors in their respective wards until outcome. Each child's daily management record was checked from files and recorded on forms.

The caregivers received pre-test and post-test counselling for HIV testing by a mature, trained and experienced multi-lingual counsellor. All laboratory findings were communicated to the caretakers and (except for the HIV test) photocopies were placed in the patients' files as soon as they became available. Significant results needing urgent attention were communicated to the doctor on duty. The caretakers of children who tested positive for HIV were counselled and advised to attend the Paediatric Infectious Disease Clinic for continuous management and follow-up.

The Fleiss sample size calculation with continuity correction was based on comparative independent proportions: a baseline case fatality of 24% and an expected outcome case fatality rate of 12% for a power of 80%, a significance level of 95% and an estimated attrition of 25% (appendix v).

3.4 Pre-period assessment

The baseline information and laboratory data were collected on admission and the children were then followed up until discharge or death. Demographic data were ascertained using a questionnaire administered to the caretaker by trained, experienced research assistants (RAs) who were fluent in both the local language (Luganda) and English. The questionnaire was combined with a checklist (Appendix iv). The study doctor interviewed the respective caregivers and filled in the questionnaire.

3.4.1 Anthropometric assessment

Height and weight are the anthropometric measurements recommended by the WHO expert committee on anthropometry for five months to 20 years of age (WHO, 1996). All measurements were taken by two trained and experienced health research assistants with prior knowledge and skills in anthropometry (figure 6). There was close adherence to standard measurement techniques, protocol and equipment. Measurements were taken in the morning to minimize inter-subject variation. A height board with a measuring range of 0-100 cm was used to measure height/length. All measurements were taken to the nearest acceptable inter-measurement difference of not more than 1 cm. An average of

two serial measurements was used. Weight was taken using a newly purchased standardised portable Soehnle Uniscale with a calibration of 100 g. The instrument was recalibrated every morning with a known fixed weight of 2 kg. Weights were recorded to the nearest 100 g and an inter-measurement difference of up to 0.2 kg was accepted. Z-scores were used for assessing anthropometric measurements as they allowed control for age and sex as recommended by the WHO expert committee on anthropometry (70). The NCHS/WHO reference chart was used as reference during screening and rechecked using the EPIINFO EPI NUT programme.

3.4.2 Clinical examination

An experienced research medical doctor took the history, examined the child and filled in the information on the form bearing the child's study number. The form was completed for each child enrolled. The information collected included age (confirmed by immunization card, baptism card, or national event and calendar), sex, history of past and recent illness, symptoms and signs of present illness and drugs received. The form also had a section for physical examination findings and diagnosis.

3.4.3 Laboratory tests

Blood and urine culture and sensitivity

A blood sample from each child was inoculated into 2 culture bottles containing brain heart infusion broth and thioglycolate medium broth and incubated at 37°C for 48 hours. Samples that became turbid were sub-cultured in blood agar, chocolate agar and crystal violet MacConkey agar plates and the plates were incubated at 37°C for 24 hours. Samples that did not become turbid after 10 days were considered negative and discarded. The Kirby-Bauer diffusion method was used to isolate, identify and characterize bacteria from blood specimens (71). Sensitivity to commonly-prescribed antibiotics was tested and graded as sensitive or resistant. Urine specimens were collected using a sterile procedure. Specimens with positive microscopic findings were cultured for bacterial sensitivity to commonly-used antibiotics.

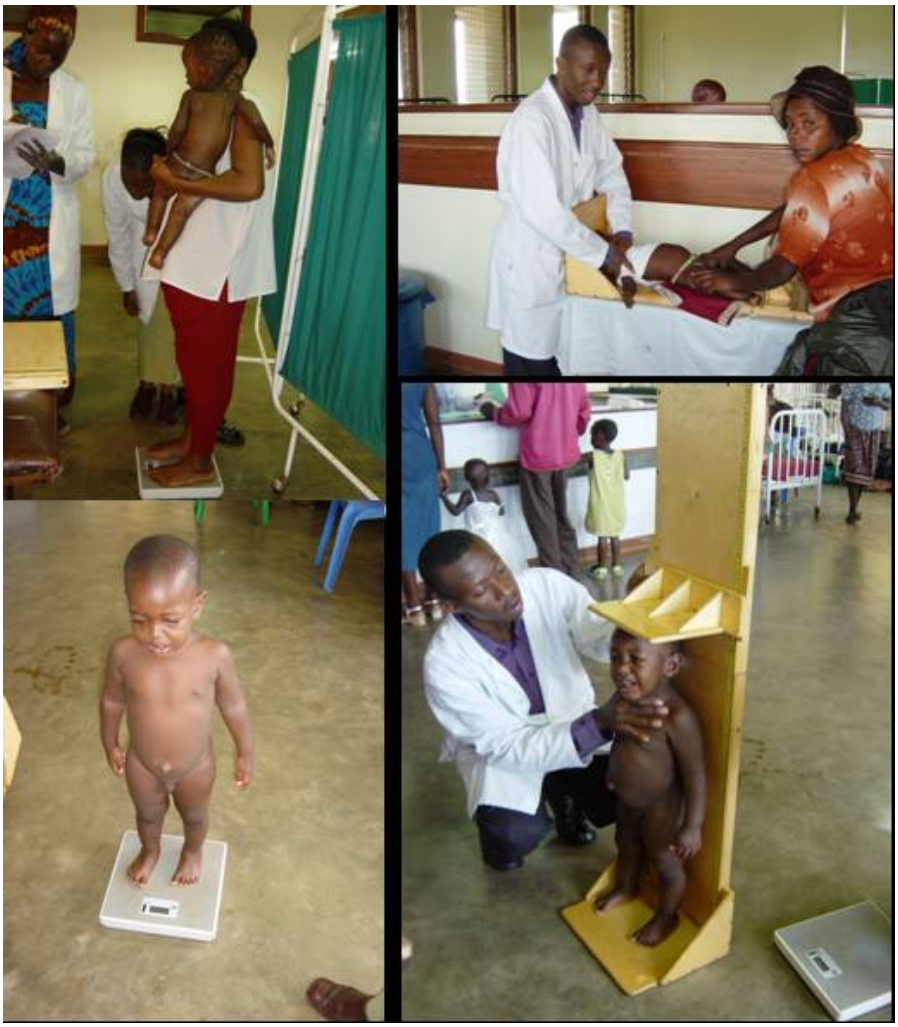

Figure 6. The research team taking anthropometric measurements of children in the Acute Care Unit, Mulago Hospital.

Haematological and biochemical tests

Haemoglobin was measured using the cyanmethaemoglobin method (72) and malarial parasites were examined in duplicate thick blood films from each specimen, stained using A and B stains and examined under the microscope. An Automated Chemistry Express Plus 550 Analyzer (Hema-screen 18, LIHD 169, S/N 802723, Italy) was used to analyse serum protein and serum albumin while serum potassium and sodium were analysed by flame photometry using automated IL 943 flame photometers.

HIV serology and cellular immunological tests

Blood was taken in 5 ml EDTA vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ USA) every morning between 8 and 11 am by venipuncture and transported within 4 hours to the Uganda Virus Research Institute (UVRI) laboratory, Entebbe for serological testing. HIV testing was performed using the standard HIV algorithm of two enzyme-linked immunoassays (EIA) in parallel. Western blotting and real-time polymerase chain reaction (RT-PCR) were performed to confirm a positive EIA test for children below 18 months old and for children with indeterminate EIA results.

TriTEST reagents (CD3; FITC/CD4; PE/CD45; PerCP and CD3; FITC/CD8; PE/CD45; Per CP) were used to stain PBMC for $CD4^+/CD8^+$ cell counting in accordance with the manufacturer's instructions. A FACScan and MultiSET software were used to perform flow cytometry and report absolute $CD4^+$ and $CD8^+$ cell counts for each specimen using a dual-platform approach (Becton Dickinson, Franklin lakes, NJ USA). Complete blood counts, including differential counts, were obtained with a Beckman Coulter Counter (73). Blood was stained within 12 hours of collection and the results were analysed within 24 hours.

3.4.4 Chest X-ray

Chest X-rays were taken once on admission to diagnose pneumonia. The reading and reporting were performed by a senior paediatric radiologist.

3.4.5 Follow-up assessment

All children in the study were followed closely during their management in the respective wards and data were collected using a follow-up form (appendix iv). Where necessary, the study provided any prescribed medication that was otherwise unavailable. The results of the investigations were delivered to the respective ward teams promptly. Outcomes were discharge, death or self-discharge. The main outcome measure for this study was death.

3.5 The improved practice

A team from the department of Paediatrics and Child Health reviewed the data from the pre-period and concluded that blood transfusion and intravenous fluid infusion were the main risk factors for mortality among children with severe acute malnutrition in the hospital. These data are presented in paper I. They developed and planned an improved practice, limiting the use of intravenous fluids and blood transfusion) that could be implemented with existing resources (appendix i).

Figure 7. A training workshop in management of severe acute malnutrition for the staff of the paediatric wards by a WHO expert.

Between November 2003 and August 2004 the planned activities were implemented (table 5). The first problem we encountered was that assessments of weight-for-height including height measurements were not routinely done in the triage room. This leads to under-diagnosis of severe acute malnutrition. Therefore, in order to make the correct diagnosis in such a setting, a scale with the option of taring and a height/length board are necessary, as well as adequate staffing to carry out the procedures.

A one-week training course on current management of severe acute malnutrition was delivered to the department by a WHO expert using the WHO training modules (61). The eighteen participants comprised nursing managers for the paediatric units and wards, paediatricians, senior house officers and nutritionists (figure 7).

After this training, the paediatricians and the nursing officers in charge of wards supervised and monitored the use of intravenous fluids. They updated new nurses, doctors and medical students during teaching sessions and ward rounds. Messages about the dangers of intravenous fluid overload in severe acute malnutrition were posted in all examination and treatment rooms (figure 8). Job aids on the indications, amount and route of administration of fluids were developed and also posted in the same rooms, and monitoring and supervision were delegated to the respective ward managers.

ReSoMal was made available for treating diarrhoea and the standard ORS was withdrawn from the nutrition unit. Routine antibiotics (ampicillin and gentamicin) were given as recommended in the guidelines. Early treatment was ensured by creating a warm room with ready meals of F 75 starter diet on admission to the Acute Care Unit. Blankets were also provided to ensure warmth especially at night. Laboratory results were dispatched to the doctors on duty as soon as they were available.

In addition, copies of the guidelines on management of severe acute malnutrition were made available to doctors, medical students and nurses. At the monthly departmental meeting, the head of department emphasized the importance of appropriate fluid use in

the management of children with this condition. A room for the children with severe acute malnutrition was identified in the paediatric emergency ward to facilitate monitoring of the patients and to provide fluids, feeds and extra warmth.

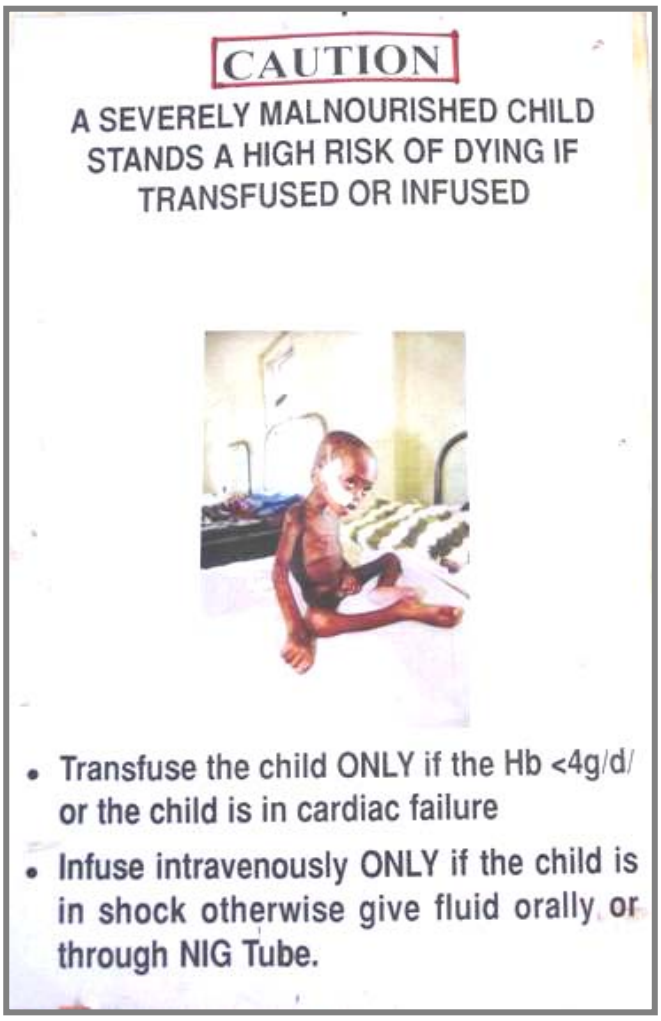

Figure 8. A poster addressing doctors and nurses at the Dept of Paediatrics and Child Health bearing a "caution" message on the use of blood transfusion and IV fluid infusion in the management of severe acute malnutrition.

Table 5. Summary of changes made in the management of severe acute malnutrition in Mulago Hospital during the study period period December 2003–August 2004.

	Previous protocol	**Changes made**
Diagnosis of severe acute malnutrition (SAM)	Wellcome classification	WHO classification • Height boards provided • Weight-for-height charts provided • Copies of guides to health staff • Staff trained
Prevention of complication	SAM not prioritized at triage No rationed feeds on admission in ACU Admitted in any of the Paediatric wards HEM for management in nutrition unit given every 3 hours Systemic antibiotic treatment with ampicillin & gentamicin for 7 days Multivitamins and folic acid tablets given daily	SAM priority cases A small side room furnished with: • warm blankets • F 75 starter diet, 2 hourly • a glucometer • Laboratory tests & results • Chest X-rays for all • Children with SAM admitted to nutrition unit
Treatment of dehydration	WHO ORS for moderate dehydration IV Ringers lactate and half strength Darrow's for severe dehydration	ReSoMal for management of dehydration Wall charts for quantity of ReSoMal according to weight IV only for those with severe dehydration and lethargy or unconscious. Filling of CMF for all children
Treatment of severe anaemia	Transfuse if severe pallor or in cardiac failure Give frusemide at start of transfusion Sub-optimally functioning side-laboratory.	Hb lab results available same day as admission or as soon as needed Job aids and caution message chart. Side laboratory functional for Hb estimation and malaria slides
Diet	High energy milk (unfortified with mineral/vitamins) in all phases. Kwashiorkor 100 Kcal/kg/day Marasmus 150 kcal/kg/day Feeding every 3 hour Rehabilitation : HEM + Porridge+ Kitoobero (multimix soft diet)	F 75- starter diet in phase 1 (100kcal/kg/day) F 100 Transition (same amount) F100 Rehabilitation (gradual increase up to 220 Kcal/Kg/day) + porridge +Kitoobero (multimix soft diet)
Monitoring	Daily weighing and plotting Respiratory rate, pulse and temperature taken twice daily. Rationed and supervised feeding	Daily weighing and plotting Respiratory rate, pulse and temperature taken every 15 minutes for children who are on transfusion or infusion Transfusion or IV rehydration done in the intensive care side room for close monitoring Evening round by doctors
Discharge criteria	Discharged when gaining steady weight and mother able to continue with care at home Follow-up in the nutrition unit or nearest health facility	Discharged on attainment of Weight for height of 85% of reference median A supplementary feeding programme within the nutrition unit to improve on follow-up

3.6 Post-period

From September to December 2004, the intervention was evaluated on 230 children with severe acute malnutrition. The same methodology was used as in the pre-period. The children were followed and assessed daily by a study doctor in the same way as before the intervention.

3.7 Data management

Data entry

The raw data were cross-checked for completeness and correct labelling, arranged in individual participants' fastened folders and stored securely in a filing cabinet. The data were then entered and stored in Epidata (www.epidata.dk). All data were stored securely in a database accessible only to the research team. Stored data included patient identification, inpatient or hospital number and study code. Anthropometric data were first analysed using EPIINFO 6.04 and later exported to SPSS 11.5 and STATA version 9 for cleaning and subsequent descriptive and statistical analyses.

Statistical analysis

Statistical analysis was done using SPSS versions 11.5 and later version 13 and STATA version 9. Statistical methods that were used for respective papers are summarised in table 6. Characteristics and health conditions at admission were compared using the chi-square test. Bi-variate logistic regression models were built on the basis of knowledge about factors affecting the outcome variable in question (mortality). Important baseline data of clinical significance that were found appropriate were included in a regression model and used for adjustment. Dummy variables were created for the categorical variables used. Cut-off points for continuous parameters were <3mmol/L for hypoglycaemia, < 3.5mmol/L for hypokalaemia, <135 mmol/L for hyponatraemia, < 5 g/dL for severe anaemia,< 3.5 mg/dL for serum albumin and < 5.5 mg/dL for hypoproteinaemia. In the modelling, the variables were chosen according to their statistical significance (P<0.2) and clinical significance. The chosen dependent variables were tested for interactions and were stratified for likelihood of effect modification.

Independent variables that showed persistently non-significant relationships with the dependent variable during modelling were excluded from the final model, while independent variables that were potential confounders and of clinical interest were retained in the final model. Kaplan Meier curves were used to determine survival functions. A log rank test was used to measure associations within and between groups. Cox's proportional hazards model was used to compare survival with and without transfusion, survival with and without infusion and overall survival between the two periods, adjusted for independent variables that were significant in univariate analysis in one of the two study periods and for covariates (sex and type of severe acute malnutrition). Time of entry was from transfusion/ infusion. For children who did not receive fluids, time of entry was a day after admission.

Table 6. Summary of the papers and their study design, sample size and statistical methods used.

Papers	Study design & sample size	Statistical methods used
Paper I	Cross sectional follow-up study of 220 children with severe acute malnutrition in the pre-period	Cross tabulation Binary logistic regression Univariate Multivariate Cox regression
Paper II	A 'Before' and 'After' design: 450 children with severe acute malnutrition, 220 pre- & 230 post-period	Kaplan Meier curves Cox regression Univariate Multivariate
Paper III	Cross sectional follow-up study including all 315 children with severe acute malnutrition (out of 450) with complete laboratory results	Chi-square Wilcoxon-Mann-Whitney test Binary logistic regression Univariate Multivariate
Paper IV	Cross-sectional follow-up study including all 450 children with severe acute malnutrition	Logistic regression Univariate Multivariate Cox Regression Kaplan Meier curves

3.8 Ethical considerations

Recruitment and investigation procedures

A total of 450 eligible children admitted with severe acute malnutrition to Mulago Hospital were recruited in the two study phases. Once a child qualified for the study, the interviewer explained the study in full and discussed the consent form with the caretaker (appendices ii and iii). The interviewer emphasised that if a caretaker chose not to participate, there would be no negative consequences and child would still get same quality of care and support. Recruitment was conducted free of coercion and the caregivers were assured of confidentiality.

Institutional review board approval

Approval was obtained from the Regional Committee for Medical Ethics, Bergen, Norway (REK Vest). This study underwent review for approval by the Department of Paediatrics and Child Health research team, Makerere University School of Medicine Institutional Review Board, Mulago Hospital Ethics Committee and the Uganda National Council for Science and Technology.

3.9 Quality control

Interviewers' training

Four interviewers were recruited with wide experience in anthropometric measurement, qualitative and quantitative research methodologies in health and fluency in both English and the commonly spoken local language (Luganda). A three day training session was held to improve the interviewers' ability to collect accurate and reliable data. Data were entered on daily basis by a data clerk and cross-checked by the PI.

Pre-testing

The questionnaires for the ACU, MNU and other wards were pre-tested to assess clarity, relevance and duration. The tools were modified accordingly.

Laboratory assessment

Laboratories were chosen on the basis of having highly trained and experienced staff, long term reputation for quality results and regular use by both local and international clinical researchers. Chest X-rays (CXR) were taken by an experienced radiographer and reports made by a senior paediatric radiologist.

4. Summary of results

To avoid repetition, this section will comprise of a summary of the results and provide an overview of them. For the details we refer the reader to the individual papers. A list of errata is attached (appendix vi).

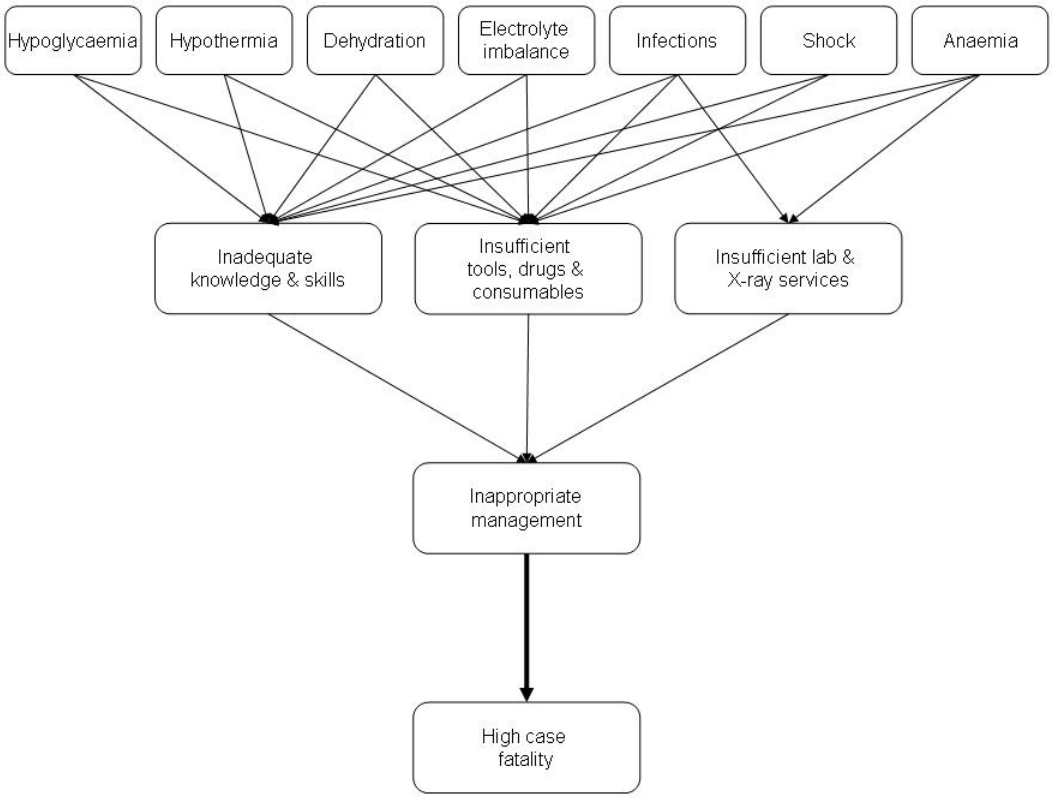

Figure 9. A conceptual framework of the factors assumed to affect the high case fatality rate of hospitalised children with severe acute malnutrition as identified in paper I.

In paper I we analysed the case fatalities among 220 consecutively admitted children with severe acute malnutrition and recorded a case fatality rate of 24%. Over 70% of the deaths occurred during the first week after admission. There were no significant differences by sex, age-group, and presence of oedema or HIV status. Twenty-four out of 52 children who received blood transfusions died, and 26 out of 62 children who received

intravenous infusions died. We established that fluid overload associated with transfusion and infusion - rather than hypoglycaemia, electrolyte imbalance or infections - influenced mortality significantly, especially in the first week after admission. Difficulties in the diagnosis of dehydration in severe acute malnutrition and in differentiating moderate anaemia from true severe anaemia posed great problems for management that led to inappropriate transfusions and IV infusions in the pre-period. The conceptual framework of the factors assumed to affect the high case fatality rate is illustrated in figure 9. Inadequate knowledge and skills in management of dehydration and anaemia in these children, coupled with insufficient laboratory resources and consumables, affected the quality of care and contributed to the high case fatality rate. The subsequent improved practice design was based on this information.

In paper II we compared the care and the outcome of children with severe acute malnutrition before and after the practice was improved by standardized use of intravenous fluids. We demonstrated that with improvement in quality of care practice through close supervision, continuous reminders and some improvements in basic supplies, the number of inappropriate blood transfusions and intravenous fluid infusions was reduced, and so was the case fatality rate during the first week after admission. However, the overall case fatality rate did not change.

In paper III we combined the data for all 450 children over the two periods to assess the effect of HIV and immunological status on outcome. One third of the 315 children with complete blood tests had $CD4^+$ cell counts below 25%. The depletion was more marked in children who were infected with HIV-1. Both granulocyte and lymphocyte suppression indicates reduced haemopoietic function, and as observed in this study, the additional burden of HIV-1 infection seems to lower the $CD4^+$ percentage further. New in this study was the observation that both HIV-positive and HIV-negative children without oedema presented with lower $CD4^+$ percentages than children with oedema. Both these observations seem to associate the development of oedema with a certain degree of

immunocompetence, which may suggest that the pathophysiology of oedema in severe acute malnutrition has an immunological aspect.

In paper IV, we also combined the data from all 450 children over the two periods to describe the pattern of bacteraemia among children with severe acute malnutrition in Mulago Hospital, Uganda. We found that 17% of the children had bacteraemia. A positive HIV test did not significantly increase this prevalence. A high proportion of Gram positive organisms, particularly *Staphylococcus aureus,* was also found. We demonstrated high bacterial resistance to commonly-used antibiotics such as co-trimoxazole, ampicillin and chloramphenicol among both HIV-positive and HIV-negative children. Such high resistance raises great concern as ampicillin, in combination with gentamicin, is routinely used as a first-line antibiotic and is given to all children with severe acute malnutrition admitted to Mulago Hospital. On the other hand, there was high susceptibility to ciprofloxacin, ceftriaxone and gentamicin regardless of HIV status. Blood isolates from HIV-infected children were more susceptible to ampicillin and chlorampenicol than those from HIV negative children. The mortality among children with severe acute malnutrition with bacteraemia was 28.9%. Overall, there was no significant association between bacteraemia and mortality. However, among the children with bacteraemia, the mortality was much higher in HIV-infected children than HIV-uninfected children with severe acute malnutrition.

5. Discussion

This thesis presents a study carried out in the paediatric wards of Mulago Hospital, situated in Kampala, the capital city of Uganda, one of the large hospitals in Africa with an unacceptably high case fatality rate of children with severe acute malnutrition. Here, as in many other African hospitals, the paediatric services are chronically under budgeted – and undersupplied with human resources – and WHO standardised care is unlikely to materialise any time soon.

Against this background, we asked ourselves: 'Can some improvements be implemented in a sustainable way with the existing resources?' The purposes of this thesis were: first, to understand the factors that are associated with the high case fatality rate in children admitted to this hospital with severe acute malnutrition; second, to plan and implement an intervention within existing resources based on the initial observations; and third, to evaluate the effect of the chosen intervention. This chapter will discuss methodological issues, the implications of the major findings and conclusions to be drawn from the study.

5.1 Methodological considerations

We chose a 'before and after' intervention design because we could not perform a randomised controlled trial (RCT), the gold standard, to determine the effectiveness of an intervention. This 'before and after' design is increasingly used in quality of care interventions where randomization is unethical or where the intervention affects the whole unit or system (75). However, the design has limitations since the outcome was assessed on two different groups of children with severe acute malnutrition, pre-period and post-period. The two groups were separated in time by one year.

Internal validity (absence of systematic error)

Given the above limitation, we designed the study to minimise the potential sources of bias, for instance to avoid seasonal variations; the season was chosen to be the same in the two periods. Similar short periods of observation were used to avoid within-period changes in patient care. There was no shortage of blood or intravenous fluids to influence usage. All eligible children formed the sample frame. Consecutive sampling was used and all children identified as eligible were included. In addition, the same data collection instrument was used for the two periods and clinical subjectivity in diagnosis was reduced by complementing with laboratory tests and X-ray reports. The same team collected the data throughout the study, thus minimising the effect of information bias. All positive cultures were reported even if they were thought to be contaminants.

Nevertheless, some factors differed between the two groups of children. The baseline characteristics were compared and there was a tendency for the second group to be more seriously ill. We suspect that this could be because a Paediatric Infectious Disease Clinic (PIDC) became operational between the two study periods, an outpatient clinic with focus on HIV-positive children. This is likely to have increased the rate of identification of HIV positive children with severe acute malnutrition on admission. However, we controlled for the effect of HIV in the analysis.

Drop-out

Another potential bias results from subjects who dropped out after being included in the study. Although we tried to ensure adequate follow-up of all the children in the study, some caregivers left the hospital without informing the staff or against medical advice. The reasons for such self-discharge could not be ascertained. There is a potential risk that this could have led to misrepresentation of the fatal outcome in either period. However, there was no difference in the drop-out rates in the two periods: 27% in the pre- and 23% in the post-intervention group. Drop-outs occurred after baseline data were collected, and mostly after a week of stay, so we included them in the analysis and compared their

characteristics with those who remained; we found no significant differences. We used survival analysis procedures to adjust for the loss to follow-up (drop-outs).

In a study such as ours, incomplete data sets (lack of pieces of information) matter as much as drop-outs. This is particularly important when running adjusting procedures such as survival analysis. In this study, only 94 and 184 cases in the pre- and post-periods, respectively, had complete data for all the chosen factors in the final model. This illustrates the fact that the data collectors were more vigilant in the second period after becoming more experienced. So this could have affected the overall width of the confidence intervals in the study but is less likely to have affected differences between the two periods observed.

Precision (absence of random error)

Precision in measurement and estimation of data corresponds to reduction of random error. This is often improved by (1) having a sizable sample and (2) increasing study efficiency. In this study, the sample size was based on comparative independent proportions (75, 76) and depended on a power of 80%, significance level of 95%, estimated attrition of 25% and a baseline proportion of 24% (20). The calculated sample size was adequate to detect an expected change from 24% among the unexposed to 12 % among the exposed case fatality outcomes (appendix v). To increase efficiency, we chose the age group below 60 months with a high rate of severe acute malnutrition and recruited them from the point of entry to the hospital.

External validity

A study is externally valid or generalizable if it can produce unbiased inferences regarding a target population. This thesis is based on findings from one single national referral and teaching hospital situated in Kampala, the capital city of Uganda. It is difficult to generalise the conclusion as valid elsewhere. Although most of the doctors working in other hospitals in the country received training in this hospital, their practices may not necessarily be similar. Blood and intravenous fluids may be more readily

available in Mulago Hospital than other hospitals. Likewise the prevalence of other factors considered may also differ.

5.2 Implications of major findings

The main findings of these studies have a number of implications and the most important are summarised in table 7. There may be other factors beyond the control of the hospital team such as accessibility and poor utilization of health services leading to delay in health seeking. However, the national nutrition policy needs to re-address the importance of assessment for acute malnutrition at all paediatric health contact points. These contact points should be equipped with colour-based mid-upper arm circumference (MUAC) measuring tapes or Weight-for-Height wall charts for screening children for acute malnutrition. This could enhance early diagnosis, referral and management of children with severe acute malnutrition.

Outpatient therapeutic care (OTC) of severe malnutrition with no complications has been implemented in emergency situations (77, 78). Some countries have adapted OTC in stable situations as well (41). There is a need to pilot OTC in Uganda. If successful, this could decongest inpatient care, reduce on workload, and improve quality of inpatient care and subsequently, lower case fatality rate. However, the management of severe malnutrition in infants less than 6 months old and children with HIV co-morbidity remains a great challenge (40).

Table 7. Summary of the most important findings in the study and their implications.

Finding	Implication
Paper 1	
Inappropriate transfusion and intravenous fluid infusion contributed significantly to high case fatality rate	• Improved practice needed to reduce attributable case fatality. • the need for a continuous in-service • training and regular updating of service providers • simple job aids for effective and quality health service delivery • the critical information in the guidelines needs to be integrated in the commonly-used modern medical/nursing textbooks
Clinical guessing of haemoglobin concentration is erroneous and hazardous	• Quick bed-side haemoglobin meters important in management
Blood and IV fluids are often in large packings.	• Small volume packs of blood/fluids important to reduce overtransfusion/overinfusion
Paper 2	
Improved practice of transfusion and fluids management improved survival of severely malnourished children during first week after admission.	• Extra caution needed during blood transfusion and fluids use in management of severe malnutrition. • Need for easier and more effective monitoring parameters during transfusion and fluid infusion
No reduction in overall case fatality rate was realised	• Causes of mortality are diverse. A more holistic approach needed for effective overall reduction in case fatality rate.
Paper 3	
The prevalence of HIV is high among children with severe acute malnutrition	• Establishing testing for HIV infection in the paediatric clinics is important for quality care
The patients' relatives did not object to HIV-testing of their sick child.	• Integrating nutrition into the care of HIV/AIDS needs to be emphasized.
Clinical manifestation of HIV-1 infection and severe acute malnutrition overlap in young children	• The guidelines need revision in relation to children with HIV co-morbidity • HIV-infected children with moderate malnutrition need extra attention
Paper 4	
Resistance to commonly-used first line antibiotics.	• Co-trimoxazole should be used only for prophylaxis and treatment for PCP. • Ceftriaxone or ciprofloxacin should be used as second line drug

5.3 Why did the improved practice not reduce the overall case fatality rate?

While this thesis was being completed we found two articles that we think can help us to interpret our findings. The first article presents a systematic approach to assessing the systemic capacity of a health system, which we will briefly summarise (79), and the second is a recent article in the Lancet - practical lessons from the global safe motherhood initiatives - that partly uses the systemic approach to assess health system capacity (80).

The first paper (79) argues that for optimal system operation, a systematic capacity-building approach is necessary. An in-depth analysis of current capacity-building approaches is presented, drawn from experiences in Asia. The authors introduce the concept of systematic capacity-building and argue that addressing all the components would lead to improved diagnosis of sectoral gaps, improved design, monitoring and effective use of resources. According to the authors, systematic capacity-building consists of nine separate interdependent components (table 8) forming a four-tier hierarchy of capacity-building needs (figure 10).

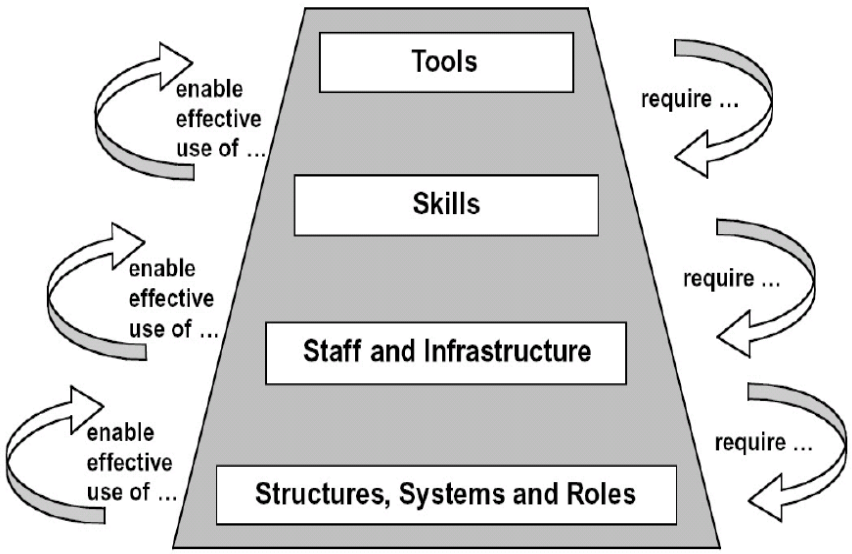

Figure 10. A systematic capacity pyramid, according to ref (79).

This concept was recently applied to four global maternal health initiatives to identify gaps and redesign new approaches for improvement (80). Millennium Development Goal number 5 is to halve the 1990 maternal mortality rate by 2015. In order to reach this goal, the global maternal health initiatives are trying to ensure that every birth is attended by a skilled health professional and that every woman who has an obstetric complication receives care either in a basic emergency obstetric care facility (typically a health centre) or in a comprehensive emergency obstetric care facility (typically a district or sub-district hospital). Halfway through this time period, large parts of the world have made very little progress towards the MDG5 goal. In fact, many countries in sub-Saharan Africa have not moved one inch – the Maternal Mortality Rate (MMR) has remained unchanged since 1990.

The authors (80) noted that capacity development often consisted of input in terms of equipment and workshops providing technical skills, i.e. the two top parts of the pyramid in figure 10, but that typically the other parts of the pyramid remained unchanged and therefore the input provided did not produce the desired improvement (figure 11). They further say:

Efforts to strengthen capacity should focus on the organisational system that 'is composed of a network of programmes of services, staff , facilities, structures (forums for discussion and collective decision making such as management boards, committees, etc), and processes of supervision, decision making, information passing, financial flows, and so forth.' When systems capacity is ignored, inputs are often wasted and results scarce. The challenge will be to address these elements of system capacity not as mechanical cogs in a wheel, but as human interactions. Effective management of these interactions needs a continual, open-minded search to understand what incentives from inside or outside any particular health system drive people — e.g., providers, patients, managers — to act as they do.

Table 8. Overview of the nine component elements of systemic capacity in relation to the situation at Mulago Hospital.

Systemic capacity	**Nine component elements of systemic capacity**	**The work to reduce the case fatality at Mulago Hospital**
Performance capacity	Are the tools, money, equipment, consumables, etc. available to do the job? A doctor, however well trained, without diagnostic instruments, drugs or therapeutic consumables is of very limited use.	Tools, consumables, Staff were trained Drugs were available Lab facility provided
Personal capacity	Are the staffs sufficiently knowledgeable, skilled and confident to perform properly? Do they need training, experience, or motivation? Are they deficient in technical skills, managerial skills, interpersonal skills, gender-sensitivity skills, or specific role-related skills?	Staff and managers trained and supervised
Workload capacity	Is there enough staff with broad enough skills to cope with the workload? Are job descriptions practicable? Is skill mix appropriate?	Insufficient, unchanged
Supervisory capacity	Are there reporting and monitoring systems in place? Are there clear lines of accountability? Can supervisors physically monitor the staff under them? Are there effective incentives and sanctions available?	Insufficient, unchanged
Facility capacity	Are training centres big enough, with the right staff in sufficient numbers? Are clinics and hospitals of a size to cope with the patient workload? Are staff residences sufficiently large? Are there enough offices, workshops and warehouses to support the workload?	Insufficient, unchanged
Support service capacity	Are there laboratories, training institutions, bio-medical engineering services, supply organizations, building services, administrative staff, laundries, research facilities, and quality control services? They may be provided by the private sector, but they are required.	Insufficient, Lab facility provided
Systems capacity	Do the flows of information, money and managerial decisions function in a timely and effective manner? Can purchases be made without lengthy delays for authorization? Are proper filing and information systems in use? Are staffs transferred without reference to local managers' wishes? Can private sector services be contracted as required? Is there good communication with the community? Are there sufficient links with NGOs?	Insufficient, unchanged
Structural capacity	Are there decision-making forums where inter-sectoral discussion may occur and corporate decisions made, records kept and individuals called to account for non-performance?	Insufficient, registered changes in a few areas
Role capacity	This applies to individuals, to teams and to structures such as committees. Have they been given the authority and responsibility to make the decisions essential to effective performance, whether regarding schedules, money, staff appointments, etc.?	Insufficient, unchanged

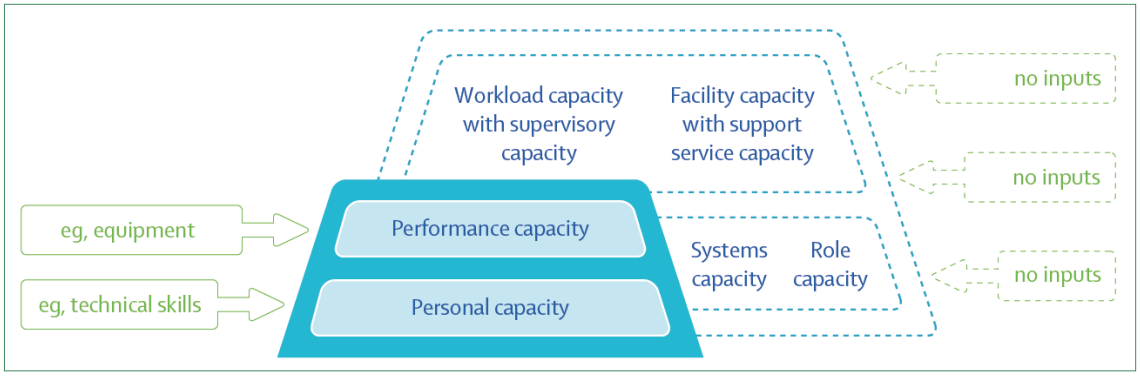

Figure 11. The components of system capacity often intervened in (front) by inputs of equipment and technical skill improvements, and the components typically left out of the intervention (back) (80). Our intervention followed the same pattern.

Our understanding is that the two situations are very similar, the global maternal health initiatives trying to reduce the maternal mortality worldwide and our efforts to reduce the case fatality rate at Mulago Hospital: both have provided the technical skills and some equipment but we have left the rest of the pyramid unchanged and now we notice with disappointment that our efforts have not produced the desired results.

In fact, the global maternal health initiatives have a strategy of standardised care that is similar to the WHO 'ten steps' strategy aimed at improving quality of clinical management and reducing case fatality in management of severe acute malnutrition to less than 10% (21, 53). However, despite improving the knowledge and skills of health workers through training, many facilities in sub-Saharan Africa have not yet attained this standard (33, 34).

Drawing from this review, we can speculate that achievement of set standards and goals in service delivery perhaps requires a health systems approach. A universal approach may not be the answer; neither is reinvention of the wheel. After learning what to do, we need to consider varying the process of implementation, taking the prevailing circumstances and conditions into consideration.

Poor performance in health sectors has also been attributed to poor remuneration of health workers (81-84). In resource poor settings, including Uganda, poorly paid, de-

motivated and over-worked health workers are forced to take up multiple jobs, often equally demanding as their primary employment. The quality of service delivered is compromised and may impact on survival of the patients. A recent randomised study in Africa introduced a standardised hospital management for malaria (85) and compared the survival of children in two different wards; in one the health workers were receiving a financial incentive when procedures were followed and in the control ward the children were managed by equally trained health workers with no extra incentives. The mortality was 5% in the ward where incentives were provided compared to 10% in the control ward. A similar improvement using financial interventions was reported in a different setting in Mexico (86). Although some professionals argue that emphasis on external rewards could further damage the health profession (87), there is a need for a deeper understanding of the effect of financial incentives – or even proper salaries – in improving hospital survival and how incentives can be used to motivate health professionals to change their behaviours and improve quality of care.

We reviewed the conceptual framework of the study (figure 9) using the systemic capacity approach (figure 10 and table 8), and realised that we may have left out the more complex and time-demanding components of capacity-building (table 8). Hence, improving performance and personal capacity while leaving the rest of the capacity components unchanged (figure 11) may not lead to an appreciable overall reduction in case fatality rate. We reviewed the conceptual framework and added the systemic components initially absent from it (figure 12). If asked how to reduce case fatalities in an African hospital setting, we would certainly also bring out the other parts of the pyramid in order to create a functioning health system in which mortality can be decreased.

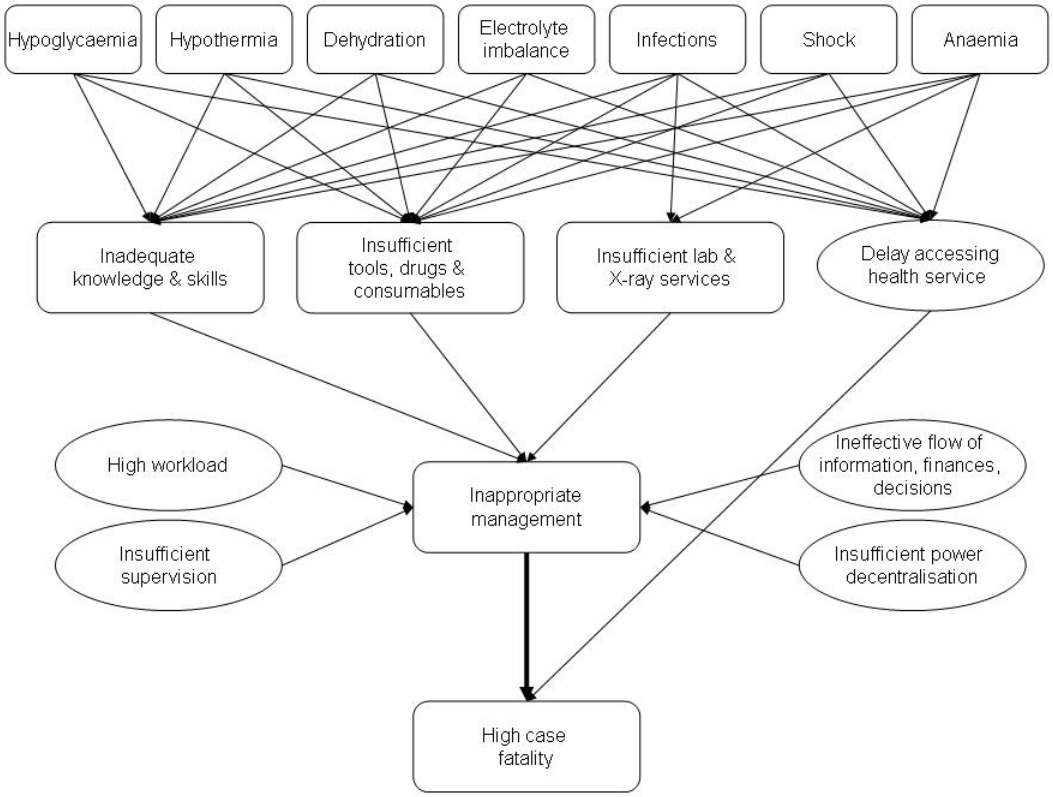

Figure 12. The conceptual framework of the factors assumed to affect the high case fatality rate of hospitalised children with severe acute malnutrition after the completion of the study, including the systemic components initially absent. See also table 8.

5.4 The silver lining for Mulago Hospital

Mulago Hospital has recently embarked on strategies to improve the quality of service delivery for children with severe acute malnutrition, addressing some key components of systemic capacity:

- Outpatient care of children with uncomplicated severe malnutrition was launched as a pilot project. This is aimed at decongesting the understaffed inpatient service and improving quality of service delivery.
- Children exposed to or infected with HIV/AIDS are managed jointly with the Paediatric Infectious Disease Clinic and enrolled in outpatient therapeutic care when they are moderately malnourished. This is aimed at preventing severe acute malnutrition.
- A close network with donor agents; UNICEF, WFP, WHO and Ministry of Health collaborate through provision of quality feeds and equipment, monthly data sharing and capacity-building to ensure continuity of quality service delivery.
- The national guidelines have been revised to improve the quality of service delivery
- Increase in sharing of information at departmental and managerial levels.
- The nutrition unit is in the process of being given semi-autonomous financial status. This will ease the bureaucratic bottlenecks that often result in procurement delays.
- The hospital has recruited and employed qualified nutritionists to boost and improve the quality of nutritional care.

There may be other factors that are beyond the control of the hospital team such as accessibility and poor utilization of health services leading to damaging delay in health seeking. However, the national nutrition policy needs to re-address the importance of assessment for acute malnutrition at all paediatric health contact points. These contact points should be equipped with colour-based mid-upper arm circumference (MUAC) measuring tapes or Weight-for-Height wall charts for screening children for acute

malnutrition. This could enhance early diagnosis, referral and management of children with acute malnutrition.

5.3 Conclusion

We note – with regret – that on its own, universal application of the WHO-recommended standardised care is far from possible in this under-resourced setting. The clinical outcomes are far from satisfactory, even with suggested relief operation standards (53), and in the end it is a moral imperative to try to improve the capacity-building approach and resource allocation for paediatric clinical care if we are going to be able to reach Millennium Development Goal number 4: to decrease by two thirds the mortality rate among under-fives in sub-Saharan Africa.

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Appendices

Appendix i. Proceedings of a Workshop held by the Department of Paediatrics, Hotel Diplomate,Muyenga 6-7 Nov 2003

Participants

Name	Designation and work place
1. Prof. Tumwine James	Coordinator, NUFU Project, Facilitator
2. Dr. Tahmeed Ahmed	Centre for Health and Population, Bangladesh, Cordinator, NUFU
3. Prof Dr. Thorkild Tylleskär	Project Coordinator, Essential Nutrition, Bergen, Chair of Session
4. Prof. Christopher Ndugwa	Paediatrician, Department of Medicine
5. Dr. Hanifa Bachou	Medical Officer MNU, PhD student, Presenter, Chair of Session
6. Dr. Robert Mwadime	Nutritionist, RCQHC, Chair of Session
7. Busingye Janeva,	Social Worker, Mulago Hospital, Presenter
8. Sr. Mary Ganaffa	SNO, In-charge, Stanfield ward, Mulago Hospital
9. Dr. Ediam Tom D	Senior House Officer, Department of Paediatrics
10. Matron Juliet Katembwe	Senior Nursing Officer, MNU
11. Dr. Jane Acan	Senior Houser Officer, Department of Paediatrics
12. Dr. Cissy Mbazalaki Mwaka	Peadiatrician, Honorary Lecturer, Department of Paediatrics
13. Dr. Sabrina Bakeera	Paediatrician, Honorary Lecturer, Department of Paediatrics
14. Dr. Victor Musiime	Senior House Officer, Department of Paediatrics
15. Dr. Juliet Nankunda. K	Paediatrician, Special Care Unit, Mulago Hospital,
16. Dr. Angel Baguma	Principal Catering Officer, Mulago
17. Dr. Elyanu Peter,	Senior House Officer, MNU
18. Dr. Arthur Bimbaza	Senior House Officer, Department of Paediatrics
19. Dr. Charles Namisi Patrick,	Senior House Officer, Department of Paediatrics
20. Dr. Charles Karamagi	Director Clinical Epidemiology Unit, Paediatrician
21. Dr. Nakiboneka Ssenabulya	Paediatrician, Mulago Hospital
22. Dr. Eddie Mworozi,	Senior Lecturer, Department of Paediatrics
23. Dr. Naamala Sengendo H	Paediatrician
24. Dr. Mugalu Jamir,	Paediatrician Mulago Hospital
25. Dr. Lubega Sulaiman,	Paediatrician, Department of Paediatrics,
26. Dr. Angelina Kakooza M.	Department of Paediatrics, Mulago Hospital
27. Dr. Esther Babirekere,	Paediatrician, Mulago Hospital
28. Caroline Namukwaya	Senior Nursing Officer, Mulago Hospital
29. Dr. Jessica Nsugwa Sabiiti,	Ministry of Health
30. Ursula Wangwe,	Ministry of Health
31. Adicho Millie	Mulago Hospital
32. Nassozi Roy	Mulago Hospital
33. Harriet N. Batuma	Workshop Secretariat

Workshop Agenda

1. Introductions
2. Sharing findings on mortality of children with severe PEM in Mulago
3. Update on management of severe PEM
4. Expert witness: Dr. Tahmeed Ahmed
5. Develop simple interventions to reduce the high mortality of children with severe malnutrition

Agenda I Item 1: Introductions
Participants were given five minutes to pair up and find out each other's names, designation, likes and dislikes which they did.

Agenda I Item 2: Participants' Expectations
Participants were given one card to write their expectations from the workshop. Through a clustering process the following were noted.

Knowledge	**Interventions to reduce mortality**
• To know causes of mortality in malnourished babies in Mulago • Knowledge on causes of mortality in malnourished children • To know the common causes of death among the malnourished children in Mulago • Receive update on nutrition management • To learn more about nutrition • To learn something new so as to influence management of nutrition in my ward • Improve my knowledge of management of severe malnutrition • To define the problems of nutrition of in paediatrics • To understand how to provide meals for malnutrition in children	• Management of severe dehydration in children with severe PEM • Feasible interventions in the department of paediatrics for malnourished children • Reduction in case fatality rate (CFR) 6 months from today • To reduce morbidity in children • Develop plan for reducing death from PEM • Fruitful discussions on emergency management of severely malnourished children • To reduce mortality in PEM • Mutual trusting attitude

Agenda Item 2: Sharing findings on mortality of children with severe PEM in Mulago
Dr. Hanifa Bachou presented her findings on **"Improving Hospital Management of Severe Malnutrition in Ugandan Children"**

"Expectations of Caretakers of Severely Malnourished Children Admitted in MHC"
Janeva Busingye (Social worker, study RA)

Summary of findings:	**Comments**
• Triage nurse should be placed in assessment centre to triage children who need to be admitted to ACU. • Doctors in ACU should be able to see all the patients between 30 minutes to 2 hours of arrival • Children transferred to the wards from ACU often get lost and lose time for treatment. They should be escorted by a nurse • The ACU should be fully functional 24 H including the side-lab. • All prescribed drugs should be available to improve on treatment • Caregivers expect results to be communicated to them. • They expect to spend a short time in hospital during rehabilitation of malnutrition. • They should be offered beddings, food for both children and adults • Caregivers should be taught how to prepare the high energy milk (HEM)and 'kitobero' • Caregivers should be treated with kindness and in all the wards • They requested for a complaint box to be placed in the wards where they can express their concern. • They expect to be given dry ration at discharge.	• Most expectations are beyond the reach of the health workers. • Are the expectations genuine or not? • The presentation depict bigger problems other than medical care • Drawing from the Bangladeshi experience five points stand and these can be improved upon: • The waiting time of 11 hours is to much • Poor communication • Shortage of supplies • Having all facilities for severely malnourished children under one roof.

Prioritizing of gaps identified in the care for malnourished children

Skills and practice	**Health worker attitude**
• Severe malnutrition not taken as an emergency • Too much IV fluids given • Management protocols not enforced in Acute Care Unit • Lack of skills • Poor provider caretaker communication • Inaccurate weight taking • Explanations of the results of the investigations • Inadequate management of malnutrition on the wards • Long waiting time before child is seen • After triage the patients take too long waiting • Inadequate resuscitation before transfer to Mwanamugimu	• Negative attitude of staff towards Mwanamugimu • Acute Care Unit and Mwanamugimu not "child friendly" (need painting) • Poor communication between staff and caregivers • Caretakers blamed for the malnutrition • Negative attitude of Mwanamugimu staff to caregivers • Inadequate communication and counseling between staff and patient guardian • Inadequate cooperation and commitment between Acute Care Unit, Mwanamugimu and wards

Agenda Item 3: Update on management of severe PEM
A powerpoint presentation by Dr. Tahmeed Ahmed. Topic **"Management of severe malnutrition in childhood: the ICDDR, B Experience"**.

Agenda Item 4. Expert witness; (WHO expert, (Dr. Tahmeed Ahmeed, ICDDR,B Bangladesh)

One minute question by individual participant	One minute answer by the Expert (Dr. Tahmeed Ahmeed)
What causes electrolyte imbalance without diarrhea?	Pathophysiology of PEM , Faulty management and Pump, Lack of co-factors e.g. management Diarrhea – worse or acidosis
What "real" support from management did you get?	Management should be actively involved in the process e.g MoH, HSSP; Management support, demonstrate what we can practically do! No wish list; If management works disseminate it – reputation – management and happy
What are reasons for self-discharge?	Competing demands, Other children and jobs
What preparations for children with P.D?	Respond to usual diet, Very few need low lactose
What drugs for deworming?	Albendazole start, Mebendazole (long time)
How do we manage both severe PEM and severe anaemia Hb<5 then transfuse?	Anaemia, PEM and heart failure, very cautious of transfusion, Furosmide, slow transfusion, no Feeding during transfusion
Ignorance, poverty and disease? What is the % of each?	I don't know
Can you diagnose kwashiorkor or oedema irrespective of Wt?	No
How do PEM children perform in the long run at school?	I have not carried out any studies on this?
What support do you give to mothers? Two hourly feeding is too intensive.	Mothers rest when staff help
Health education of father? What? Do you encourage entire family to come for counseling?	Family - birth spacing
Clarify on use of ampicillin versus oral amoxylin? Is it effective?	Yes - Oral ampicillin not well observed also 6 hourly treatment
Choice of antibiotics? Why GENTA? AMP? Based on studies.	**No**
Do you combine chlorophenical + GENTA?	Yes – no response in 24 hours, we do not do this
Choice of antibiotics what is outcome of AMP+ GENTA?	Children on chlorophenical do well
Diarrhoea	Type of diarrhea clinically, dysentery tenesmus shigella
Severe PEM and diarrhea should we know the aetiology?	Aetiology for diarrhea not for individual children but for majority e.g. cholera
Quinine IV – how do you handle in severe PEM?	Avoid too much amount to avoid overload
Any challenges with PEM/HIV in your country?	HIV prevalence is very low in Bangladesh
Clarify on blood transfusion	Blood transfusion should never be a routine, Only if indicated e.g. in severe anaemia, If Hb < 5g/l,.Very slowly 10 ml/kg in 3 H
Hepatomegally as a risk factor for death?	Many others. Why? Increases the chances of death
What are the sources of micronutrients?	Not adding to feed
Could buy CMV mix?	Don't know
When is best time to start health education?	When stable – Mwanamugimu
Do you still use chicken feed?	Milk based, Suji (rice based), Chicken (minced), Pro-sobee
How do you reduce the duration of stay?	Revisit protocol, Assess if you are providing appropriate treatment Micronutrients may be growth limiting, there is need to look at protocol
How do you follow to prevent relapse?	Counsel – follow up benefits, Importance of micronutrients, Compliance to follow up is poor
Is management for neonate marasmus the same?	No consensus
Criteria for discharge?	Weight gain rate implied WHL 80%
Free radical theory	Kwashiorkor versus marasmus, Read it up
Socio demographic data	Education = 0 = marriage = ??
Severe anaemia and severe dehydration approach?	Poor vital signs – fluids, Arrange for blood If heart failure – use packed cells over 3 hours

Clarify importance of "one roof"	Logistics (nurses and doctors), Caretakers (Rain, use Mulago experience and location)
Could "one roof" be related to specialization?	Never dismantle what you have – fine tune strategy

Identified gaps in care for malnourished children at Mulago hospital by Participants

Protocols and guidelines	**Equipment and supplies**	**Management and administration**
• Lack of job aids for health workers • Lack of official protocol • Treatment protocol does not always follow recommended guidelines	• Poor laboratory service in Mulago hospital • Weighing scales not standardized • Inadequate sundries • No feeds for malnourished children in ACU • More resource allocation needed i.e. for providing feeds to children • Lack of emergency drugs and equipment • Inadequate supplies like water, drugs and blood • No Oral Rehydration Salts in Acute Care Unit	• Inadequate personnel • Inadequate support by management • Lack of in-service training • Absenteeism of senior staff of Mwanamugimu • Management does not prioritize malnutrition • Twenty-four hour lack of coverage of wards and teenage place • Poor feeding of children with other ailments – children thus get malnourished on the wards • Lack of one roof • Lack of good inter-ward referral system Poor ward (MNU) coverage by doctors

Skills and Practice

- Inappropriate practice
- Children not kept warm
- Over use of injections
- Too much IV fluids given
- Children not kept warm in ACU
- Poor injection control on the wards
- Lack of skills
- Management protocol not enforced in ACU
- Inadequate patient hand over
- IV injection not well monitored
- Inappropriate blood transfusion
- Potassium not routinely given
- Poor provider caretaker communication
- Treatment and skills
- Clinicians do not take the anthropometrics measurements of patients
- Delayed treatment
- Inadequate monitoring during the immediate admission period
- Absenteeism of senior staff of MNU
- Long hospital stay
- Lack of service training
- Lack of follow up after discharge
- Inadequate weight taking
- Inadequate resuscitation before transfer to MNU
- Inadequate management of malnourished on other wards
- Zealous infusion/transfusion of children with severe PEM
- A system in Assessment to identify medical patients who should be seen in ACU

Eequipment and supplies

- Poor laboratory service in Mulago hospital
- Weighing scales not standardized
- No resuscitation equipment in MNU
- Lack of feeding equipments e.g. cups
- Lack of NGT
- Lack of warming facilities e.g. blankets
- Lack of stimulating toys for admitted malnourished children
- Inadequate sundries
- Inadequate food
- No feeds for malnourished children in ACU
- Inadequate drugs
- More resource allocation needed i.e. for providing feeds to children
- Lack of emergency drugs and equipment
- Inadequate supplies like water, drugs and blood
- Lack of multi-macro nutrients supplementation
- No Oral Rehydration Salts in ACU

Health workers attitude

- Human aspects of care
- Too many caretakers run away due to health workers attitude
- Caretakers blamed for the malnutrition
- Inadequate communication and counseling between staff and patient guidelines
- ACU and MNU not "child friendly"
- Poor communication between staff and caregivers
- Negative attitude of staff towards MNU
- Negative attitude of MNU staff to caregivers
- Lack of compassion to the affected attendants
- Inadequate cooperation and commitment between ACU, MNU and Paed. wards
- To be treated humanely

Community K.A.P

- Social stigmatization towards malnutrition
- Delayed presentation
- Disease
- Community perception of MNU i.e. for the poor
- Ignorance
- Poverty
- Disease
- To many caretakers runaway

Protocols and guidelines

- Lack of official management of protocol
- Lack of proper criteria for admission to MNU
- Lack of job aids for health workers
- Lack of treatment guidelines for pneumonia among malnourished children
- Treatment of protocol does not always follow recommended guidelines
- Resuscitation guidelines are lacking
- Limited research

Management and administration

- Lack of good inter-ward referral system
- Distance between MNU and other wards
- Distance from ACU is too long
- No play/stimulation facilities for children
- Poor patient research for admitted patients
- Management does not prioritize malnutrition
- Nutrition not priority area for hospital management
- Lack of place on the ward allocated for SAM
- Overall management not optimized – need for more accountability
- 24 H lack of coverage of wards & teenage place
- Poor ward (MNU) coverage by doctors
- Absenteeism of senior staff of MNU
- Lack of line of flow for SAM malnourished admitted children
- Poor staffing (limited number of staff, Inadequate personnel)
- Lack of one roof
- No special isolation area in emergency ward
- Inadequate support by management
- Lack of continuous medical education
- Lack of in-service training
- Poor feeding of children with other ailments – children thus get malnourished on other ward

Agenda Item 5: Develop simple interventions to reduce the high mortality of children with severe malnutrition & Expected outcome

Participants identified three expected outcomes (below) with each star indicating one's choice of preference.

1. Decrease the CFR within six months	**********
2. Decrease duration of stay	***
3. Reduce the readmission rate	*

Participants agreed that the expected outcome for this workshop would be to reduce CFR within six months. After six months another workshop would be organized for participants to review the outcome.

What needs to be done to reduce CFR in six months?

Process	Outputs	Outcome	Support
Protocol of care by all health workers in paediatrics • Appropriate accurate anthropometry taken • Feed child every 2 hours (F75) on admission in ACU and all wards • Work out antibiotic of choice • Use appropriate buckets to store ORS	• Less than 40% receiving IV • All children on potassium and zinc • All children to have controlled temperature (warming routine) • Feed within 2 hours of admission • All children will be on folic acid • Appropriate routine antibiotics for all children • All children will be on folic acid • All caretakers will be provided with a key message to decrease CFR	**Reduce CFR**	• Develop a protocol by 15th December 2003 • Reshuffle/deploy Mwanamugimu staff • Update new staff in paediatrics on protocol use • Update existing staff of all protocol use in paediatrics • Have F75/F100 in all wards according to needs (priority – ACU & MNU) Mwanamugimu) • Make supplies (especially ORS available) • Make monitoring cards

Group 4: Potocol and guidelines: ***Task group: T. Thorkild, T. Ahmed, H. Bachou and Mugalu J***

What needs to be done	By when	By who	Resources	Indicators
1. Revise protocol of care	By 15th Dec 003	J. Tumwine, T. Thorkild U. Wangwe, C. Mbasaalake J. Nsungwa, A. Tahmeed H. Bachou. J. Mugalu	+	Revised protocol document in place
2. Develop job aids for health workers (Wall charts)	By 15th Dec 003	H. Bachou, C. Mbasaalake A. Tahmeed, J. Mugalu	+	Job aids in place – all paediatric wards
3. Sensitization of	By 22nd Dec 003	J. Tumwine, C.	+	Number of people and number

peadiatric health workers (3 meetings) - Paediatricians + SHOs - Interns + M.O + CO - Nurses		Mbasaalake J. Katembwe, C. Namukwaya H. Sengendo, H. Bachou H		of meeting held
4. Use of protocol by all staff	1st Feb 2004	All peadiatric health workers	0	1. N0. of children managed according to protocol 2. N0. of peadiatric health workers conversant with the protocol

Group 3. Health workers attitude

What needs to be done	By when	By who	Resources	Indicators
1. Simple and friendly interaction between health workers & caregivers/patients Good reception/greetings Praise where necessary, compassionate Don't blame	2 weeks	Nurses, doctors, J. Busingye, lab tech, support staff and others	0	Exit interviews Improved health care giver relationship
2. Orientation of caregivers in different units	2 weeks	Nursing staff, ward LCs	0	Exit interviews Number of caregivers oriented
3. Simple explanations of procedure and activities + child condition	2 weeks	Health workers	0	Exit interviews Explanations understood
4. Effective visual aids to communicate messages	2 months	IEC unit, MoH	+	Availability of visual aids on unit
5. Encourage team work & professionalism + meetings			0	No. of meetings held in the month
6. Increased support supervision	2 weeks	Supervisors and management	0	No.of support supervision visits made (conducted)
7. Training on communication skills, counseling, public relations and customer care	1 month	Personnel	+	No.of training sessions held
8. Job description guides	1 month	Direct supervisors/personnel	0	No. of staff informed about job descriptions
9. Provide/develop key messages to caretakers	7/11/2003	All members of this group and workshop team	0	Key messages developed

Messages to care givers	Outputs	Support systems
1. Feed child every 2 hours 2. Keep child warm 3. Follow instructions/advise given by health worker 4. Report any change in child's condition immediately (identify change signs) Talk to us, we are here for you	1. Improved health worker attitude 2. All caregivers will be provided with a key message to reduce CFR 3. Improved patient care	1. Proper job descriptions 2. Support supervision 3. Regular meetings (weekly) 4. In-service training on communication skills 5. Psychosocial support to health workers

Group 1. Management and administration, equipment and supplies: ***Task group: A Baguma,*** *H. Ssengendo, A. Mpimbaza, D. Ssenabulya, S. Lubega, J. Nankunda*

What needs to be done	By when	By who	Resource	Indicator
1. Milk supply to all wards	By Dec 2003	A. Baguma	++	Record of milk received in ward
2. Training and management protocols on equipment use	By end Jan 2004 CME	H. Bachou	+	Number of people trained
3. Advocacy (milk, drugs, ORS)	11/11/2003	Head of department & head of unit	0	Supplies and equipment
4. Requisition of adequate supplies and equipment, drugs and water	17/11/2003	Ward 16: Namukwaya W ard 1C: M. Adicho, MNU: Juliet ACU : J. Nankunda, Ward 16: Peninnah	0	Order book requisition of supplies received
5. Health workers supervising feeding	By Dec 2003	Ward 1/C	0	Feeding charts

Outputs	Progress	Support
1. Emergency treatment of all children with SAM in ACU 2. Twenty-four hour functional ACU 3. Good inter-ward referral system 4. Full commitment of health workers in MNU	1. Active screening for SAM PEM triage at ACU 2. Special room for management of children with severe PEM in ACU and other wards 3. Enforce 24 hour coverage of ACU lab 4. Resident intern in MNU for 24 hours 5. Closer supervision of interns, SHOs & senior staff in MNU	1. Supply all wards and ACU with milk 2. Training staff on management and use of equipment 3. Advocacy for support (increasing allocation of children feeds) 4. Adequate supplies, drugs e.g. ORS 5. Supervised feeding of severely malnourished children

Group 2, **Skills and attitude**

What needs to be done	By when	By who	Resource	Indicators
1. All severely malnourished children should be classified as RED (emergency)	21st Nov 2003	Sister in-charge ACU	0	Proportion of severely malnourished classified as emergency
2. Allocation and use of specific space for patient flow and management	1st Dec 2003	Sister in-charge ACU Doctor in-charge of ACU	0	Availability of space Proportion of severely malnourished children who use space
3. Record time of triage and starting of treatment	1st Dec 2003	Triage nurse Treatment nurse	0	Proportion of children who will have the two times record
4. Train staff in paediatrics on assessment and management of dehydration in severely malnourished children	Existing staff by 1/01/2004 New staff by 14/2/2004 and 14/4//2004	H. Bachou	++	Number of staff trained
5. Appropriate weighing technique i) Balancing scale before each weight ii) Use of appropriate scale for age	21/11/2003	Triage nurse	+	1. Check after 6 months 2. Weighing technique has improved

iii) Weighing children nude iv) Regular librations of scales				
6. Establish criteria for transfer to Mwanamugimu	1/01/2004	H. Bachou	+	Written criteria in ACU
7. Provision of feeds to all paediatric wards	1/04/2004	A. Baguma	++	Availability of feeds
8. Establish feeding corners on peadiatric wards	1/04/2004	Sisters in charge	0	Presence of feeding corners

Conclusion

Assoc. Prof. James Tumwine thanked the participants for their deliberations and presented summary of the two-day proceedings

What sticks out of Dr. H. Bachou's study?	**Priority themes of the workshop**
• Hypokalemia was the most common cause of death among children in Mulago hospital • Half of the deaths in Mulago hospital are non-Mwanamugimu deaths • Use of IV fluids is quite common and is associated with a number of deaths • Three quarter (75%) if these children die within the first week of admission • HIV among malnourished children was not related to increased mortality on the wards • Inaccurate weights taken by the nurses • Hypothermia • Approximately 20% mortality in MNU • Hypoglaecemia • Malaria is not so critical in our environment for these children • No milk in Acute Care Unit • Most children die due to IV fluids and lack of potassium • Study is not yet complete (these are preliminary findings).	• Reduce mortality • Stop inappropriate use of IV fluids/blood • Severe malnutrition to be taken as an emergency • Increase advocacy for milk and medicine • Train in assessment and management • Make and make available protocol for management of severe malnutrition • Talk to staff to improve communication • Special corner for severely malnourished children • Two hourly feeding and use of F75 • We shall keep children warm • Improve weighing techniques • Communicate key message

Evaluation of the workshop

	1	**2**	**3**	**4**
The process/facilitation			***	**********
Content			********	**********

Appendix ii. Consent Form

Makerere University Department of Paediatrics and Child Health- Mulago Hospital.
Serial number_____, Name/Initials_____, Age_____
Improving Management of Severe Malnutrition in Children admitted in Mulago Hospital, Uganda: A Quality Improvement Approach.
Background/Purpose
We are carrying out a study in children with severe malnutrition presenting to AC, ACU and MNU, The purpose is to find out ways of improving the management of children with severe malnutrition.
We also want to understand how children who have HIV germs on top of severe malnutrition behave when treated for severe malnutrition. We hope to use the information to help know if your child has germs causing HIVÀIDS in the blood. At the moment there is no cure but there is a clinic in Mulago where children and adults who have the HIV germs can receive care. The study will be conducted during the period of your admission. We plan to enrol a total of 500 children, 250 at the beginning of the study and 250 towards the end of the study.

If you agree to join the study, the following will occur:
The research doctor will ask you about the child's health, medical history social history and family history. She will also ask you about history of past and current treatment your child is receiving and some series of questions. It will take about 30 minutes to complete the interview.
The child's blood will be taken and tested for cell counts red, white and infection fighting cells and presence or absence of germs that cause HIV.
The research doctor will be allowed to record information from your child's medical records.
Follow up visits after your discharge will allow the research doctor to review your child's health and growth.

Risks/Discomfort
The risk associated with the study is from drawing blood. The blood sample of about 2 teaspoons of blood will be taken using a small needle in a vein in your arm, this usually causes minimal pain. The child may develop some bruising, bleeding or infection where the needle was inserted. The same risk is also experienced with routine clinical care. Loss of confidentiality may also occur.

Benefits
X-ray and Laboratory tests in addition to the tests routinely done in the ward will be done at no cost to you. This will include CXR, Test to find out presence or absence of germs causing HIV/AIDS, measurement of infection fighting cells called CD4 CELLS, level of types of some foods required by the body. The results will be available through the research doctor who will be available in MNU.
If you accept to join the study, you will be counselled about the HIV test, if after being well informed, you consent for your child's blood to be taken. You will be counselled again when the results come back, before you are given.
We intend to this information will help provide better health care for children like yours.

Assurance of confidentiality
Every effort will be made to keep records as confidential as possible within limits of the law. All information gathered and tests done, especially for HIV will be considered confidential, Research records will be stored in locked files and only authorised persons will have access. The information that identifies your child will not be included in the reports or written articles. The files may be made available to study monitors and ethic monitors at Mulago hospital and the ministry of health for review of study procedures.

Alternatives to participation
Your child's participation in this study is completely voluntary. You are free to decide not to have your child participate in any of or all parts of the study (interview or sample collection) at any time. If you do not participate, it will not affect your child's medical care, now and in the future.
Cost/compensation
There will be no extra cost for your child to participate in this study. You will not be paid to participate in this study.
Medical care for injury or illness
The procedure used in this study is the same as routine medical care. Your risk of illness is minimal.
However, if you are injured by participating in the study, no money will be available to pay you. But, treatment and advice will be made available. If you experience any problems related to the study, please report immediately to the persons listed in the following section.
Questions/ point of contact
If you have any questions, please ask. We will do our best to answer them. If you have additional questions or if you need to discuss any other aspects of the study, please feel free to contact the following:
For questions about the study, contact Dr Hanifa Bachou- Mwanamugimu Nutrition Unit, Mulago Hospital. Mobile 077421345 0r
Dr Robert Mwadime, Regional Center for Quality of Health Care, Medical School, Mulago Mobile 077 517438 or
Prof. James Tumwine, Department of paediatrics, Mulago Hospital Mobile 077 494120

If there is any part of this consent you have not understood, please ask the investigator before signing. You will receive a copy of this consent.

Appendix iii. Statement of Participant consent

I, _____age____,
Caretaker to child _____aged_____ Relation to child _____ have been asked to participate in a research study named *Improving Management of Severe Malnutrition in Children admitted in Mulago Hospital, Uganda: A Quality Improvement Approach.* The Principle researcher, Dr Hanifa Bachou, or the study doctors or their representative _____ has explained this study to me; I understand how long it will last, what testing my child will undergo, and the risks that may be involved. The information above has been read to me, I have been given opportunity to ask questions about the research project. All questions were answered in a way that I understand, if I have any questions about this research, I can ask the study representative, _____, the study doctor named above or Dr Hanifa Bachou. I understand that my child's participation in voluntary and that I can decide not to be in the study or leave the study at any time. If I decide not to participate or leave the study, my child will not lose any benefits or access to health care. I am signing my name below to indicate my consent to participate in this project. I may keep a copy of the signed consent form.

_____ _____
Signature of Caretaker Date
(Thumb Print if non-literate) _____
Printed name of Care taker

_____ _____
Signature of Witness Date

_____
Printed Name of Witness

_____ _____
Signature of Investigator eliciting consent Date

Appendix iv. Observation Form

Improving Hospital Management of Severe Malnutrition in Ugandan Children: A performance Improvement Approach

Instruction: This questionnaire has a total of 11 pages (back to Back) containing a total of 17 questions, some sections and contain subsections with both closed and open-ended questions.
The closed ended questions have two options, Y (for 'yes') or N (for 'no') questions.
Please circle the correct response: Y (for yes) and N (for No). And write correct and appropriate information for the open ended sections in space provided.

The validation section will be filled by the Principal Investigator only.

a. Dates of Observation: ____/_____/____ to ____/_____/____

Facility Name _____
Interviewer No._____ Child's Age (months) _____Child ID No. _____ (ACU) Child ID No._____(MNU) Relation to Caretaker_____Age of Caretaker_____(Years) sex_____

b. Village_____Gombolola_____Saza_____
_____

c. District_____

d. Date of Admission: ____/_____/____ (ACU) Time of Admission
_____

e. Date of Admission: ____/_____/____ (MNU ward 2) Time of Admission
_____

f. Date of Admission ____/_____/____ (MNU ward 1) Time of Admission
_____

Date of Discharge: ____/_____/____(MNU)

1 **Interpersonal communication**

A Does the health worker explain the child's health condition to caretaker	N/A	Y	N
B Does the health worker explain the reason for admission to ward1	N/A	Y	N
c Does the health worker explain to the mother why child should be kept warm at all times especially at night?	N/A	Y	N
d Does the health worker explain to the mother why child should now be given additional food, type and number of feed and drink?	N/A	Y	N
e. Does the health worker explain to the mother why child should be given the feed frequently and according to schedule both day & night	N/A	Y	N
F Does the health worker ask an open-ended question to verify the comprehension of the child care?	N/A	Y	N

Treatment

2 What does the health worker administer or prescribe for the child?							
a Immediate referral? Y N							
B	Antimalarial injection Drug----------	Y IM	N IV	i	ORS/ ReSoMal How much? ---------- Other fluid----------	Y	N
C	Antimalarial Tb/syrup Drug----------	Y	N	j	Antidiarrheal Drug----------	Y	N
D	Paracetamol Tab/syrup	Y	N	k	Antibiotic tablets/syrup Drugs----------	Y	N
E	Tepid bath	Y	N	l	Antifungal tablets/syrup Drug----------	Y	N
F	Antibiotic injection Drugs---------- Given IV	Y	N	m	Folic acid tablet Dose----------	Y	N
G	Vitamin A	Y	N	Iron Tablets/syrup & Dose			
H	Multivitamins tablet/syrup			Other (specify)----------		Y	N

Feeding

What does the health worker prescribe as feed for the child & how has child been fed?							
a Check the time child arrived in ward 3 & time child received first feed or drink (glucose milk or other) **Duration _____ minutes**							
b	**2) F-75** How much? ---------- How frequent? ----------	Y	N	f	**3) Given F-75** How Much---------- How many times? ---------- How given?---------- Completed?	Y Y	N N
c	**4) F-100** How much? ---------- How frequent? ----------	Y	N	g	**5) Given F-100** How much---------- How many times? ---------- How given?---------- Completed?	Y Y	N N
d	**6) Whole fresh milk** How much? ---------- How frequent?----------	Y	N	h	**7) Given whole fresh milk** How Much---------- How many times? ---------- How given? ---------- Completed?	Y Y	N N
e	Porridge How much? ---------- How frequent? ---------- ---------- Ingredients---------- Consistency----------	Y	N	i	**Kitobero (specify)** How Much---------- How many times? ---------- How given?---------- Completed? consistency	Y Y	N N
Comment							

Monitoring

4 ***How does the health worker monitor child's condition & what action taken?***					
a	Records temperature 6 hourly Other (specify)----------	Y N	**h**	Body temperature < 35.5 axillary Body temp. > 37.5 axillary----------	
b	Checks on reduction of diarrhoea		i	*Dirrhoea still persistent*----------	
c	Checks for loss7reduction of oedema		j	If level of oedema increasing----------	
d	Reviews child's weight chart, CCP and food intake chart Other (specify)----------	Y N	k	Weight increasing with oedema ---------- Weight stagnant or decreasing with no oedema after Weight gain less than 5gm/day----------	
e	Checks on improvement of dermatosis Other----------	Y N	l	Dermatosis still increasing or wet---------	
f	Checks on child's appetite		m	Child does not finish amount of feeds measured per feed ----------	
g	Records amount of feeds actually taken each day ----------	Y N	n	Child needs more feed after finishing measured amount ----------	
Other					

General information

(Tick applicable9	N/A	Y	N
a Discharge within a week's time Other (Specify)_____ b Reason for discharge_____ c Date of Discharge _____ d Weight at discharge_____ e Appetite at time of discharge(very Good, good, fair, poor)_____			
Any other comment			

F Investigations (Lab, X-ray etc)

Type of Investigations	**Date specimen requested**	**Date specimen taken**	**Date results received**

g Medication

Type of medication prescribed	*a) When prescribed*	**When received**	**Source (Unit, other ward or caretaker)**

h Feeds

Type of Feeds prescribed (**HEM, Fresh cow milk, soy, yoghurt, porridge, Kitoobero,adult food)**	Date	Type of food prepared/served (ingredients)	Source (unit, Caretaker, other Specify)
Comment on feed supervision			

8) **Validation (Circle applicable)**	***N/A***	***Y***	***N***
10 Rehabilitation of severe Malnutrition has received appropriate management			
9) **Feeding given appropriately and adequately**			

Weight on transfer to ward 1_____, Weight on discharge_____
Height on admission to ward 1_____cm, Height discharge_____cm

Appendix v. Sample size calculation (Source: **www.openepi.com**)

(b) Sample Size for Cross-Sectional & Cohort Studies & Clinical Trials

Two-sided significance level(1-alpha):	95
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	0.96
Percent of Unexposed with Outcome:	24
Percent of Exposed with Outcome:	12
Odds Ratio:	0.43
Risk/Prevalence Ratio:	0.5
Risk/Prevalence difference:	-12

	Kelsey	**Fleiss**	**Fleiss with CC**
Sample Size - Exposed	163	162	178
Sample Size-Nonexposed	156	155	171
Total sample size:	319	317	349

Appendix vi. List of Errata

Location	Reads	Should read
Paper I		
Page 1, Abstract, Result, line 4	(OR =2.6, 95% CI = 0.8 – 8.6).	(OR =1.9, 95% CI = 0.8 – 4.4)
Page 1, Abstract, Result , line 5	(OR =5.0, 95% CI = 2 – 12);	(OR =5.1, 95% CI = 2 – 12);
Page 3, Figure 1, level 3:	618 wasted	618 wasted and/or oedema
Page 3, Figure 1, level 4:	236 wasted	236 wasted and/or oedema
Page 3, Figure 1, level 6:	165 discharged	168 discharged
Page 4, Statistical analysis**,** para2, line 2:	….significance of P<0.05, …	….significance of P<0.2, …
Page 7, Table 4, title, line 4:	Outcome of…….[25]	Outcome of ……
Page 7, Table 5, title, lines 1,2, 4	….malnourished children with diarrhoea at admission …[25]	….malnourished children with known hydration status at admission …..
Page 7, Figure 5, title, line 5	(Table 2)	(Table 3)
Paper III		
Page 4 Result, Para 5, line 3:	...CD4+ and $CD8^+$ percentages...	….CD4+ and CD4/CD8+ ratios….
Page 5, Table 4, row 2, line 5:	Monocytes 10^9 L	Monocytes 10^6 L
Page 6, Discussion, para 4, line 8:	……1 in 12 in the HIV uninfected children with oedema	……1 in 12 in the HIV uninfected children.
Page 6, Table 5, column 4, row3:	171(99)	148 (86)
Page 6, Table 5, column 4, row 4:	0(0)	15(8)
Page 6, Table 5, column 4, row 5:	1(1)	10(6)
Paper IV		
Page 3, result, para 2, line 2 :	…no significant difference in the proportion of children……	…no significant difference in children…..
Page 3, table 1, title, line 1:	...diagnosis and outcome of...	… and diagnosis of...
Page 6, Figure 1. title, line 1:	.....blood culture positive and blood culture negative result	…..Blood culture positive (left) and blood culture negative (right) results

Paper I

BMC Pediatrics

BioMed Central

Research article

Risk factors in hospital deaths in severely malnourished children in Kampala, Uganda

Hanifa Bachou*[1,3], James K Tumwine[1], Robert KN Mwadime[2] and Thorkild Tylleskär[3]

Address: [1]Department of Paediatrics and Child Health, Makerere University, P O Box 7072, Kampala, Uganda, [2]FANTA/Regional Centre for Quality Health Care, Makerere University, Kampala, Uganda and [3]Centre for International Health, University of Bergen, Norway

Email: Hanifa Bachou* - hanifa.bachou@student.uib.no; James K Tumwine - jtumwine@imul.com; Robert KN Mwadime - rmwadime@rcqhc.org; Thorkild Tylleskär - thorkild.tylleskar@cih.uib.no

* Corresponding author

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Abstract

Background: Although the risk factors for increased fatality among severely malnourished children have been reported, recent information from Africa, during a period of HIV pandemic and constrained health services, remains sketchy. The aim of this study has been to establish the risk factors for excess deaths among hospitalized severely malnourished children of below five years of age.

Method: In 2003, two hundred and twenty consecutively admitted, severely malnourished children were followed in the paediatric wards of Mulago, Uganda's national referral and teaching hospital. The children's baseline health conditions were established by physical examination, along with haematological, biochemical, microbiological and immunological indices.

Results: Of the 220 children, 52 (24%) died, with over 70% of the deaths occurring in the first week of admission. There was no significant difference by sex or age group. The presence of oedema increased the adjusted odds-ratio, but did not reach significance (OR = 2.0; 95% CI = 0.8 – 4.7), similarly for a positive HIV status (OR = 2.6, 95% CI = 0.8 – 8.6). Twenty four out of 52 children who received blood transfusion died (OR = 5.0, 95% CI = 2 – 12); while, 26 out of 62 children who received intravenous infusion died (OR = 4.8, 95% CI = 2 – 12). The outcome of children who received blood or intravenous fluids was less favourable than of children who did not receive them. Adjustment for severity of disease did not change this.

Conclusion: The main risk factors for excess hospital deaths among severely malnourished children in Mulago hospital include blood transfusion and intravenous infusion. An intervention to reduce deaths needs to focus on guideline compliance with respect to blood transfusions/infusions.

Background

Under-nutrition is associated with >50% of all childhood mortality in developing countries [1,2], with the risk of mortality being 5–8 fold among severely compared to moderately malnourished children [3]. Because of the high risk of death, most severely malnourished children are managed in hospital. Unfortunately, the number of children hospitalised with severe malnutrition continues

to rise in sub-Saharan Africa [4,5]. For instance, in Mulago Hospital, Uganda's national referral hospital, the number of children suffering from severe malnutrition increased from 11 to 45 per 1000 paediatric admissions between 1995 and 2002 [6]. Likewise, the case fatality rate increased from 15 to 24%. The case fatality rate in some African countries is >50% [7].

Factors contributing to the high case fatality in children hospitalized with severe malnutrition include acute bacterial infections, electrolyte imbalance, and micronutrient deficiencies [8-11]. Although prompt and appropriate treatment of severely malnourished children should reduce case fatality [9,12-14], no hospital study in sub-Saharan Africa has demonstrated a reduction of the case fatality to an acceptable international level of <5% – as reported, for example, in Asia [15], for which there can be several possible explanations. The difference observed may be in the stage at which the affected patients are brought for care, in the application of the clinical guidelines, or in the prevalence of HIV/AIDS [12,14,16,17].

Few studies have examined the potential risk factors for mortality among severely malnourished children admitted in African hospitals. This information is critical for the development of national guidelines for quality care of severely malnourished children. We therefore studied severely malnourished children admitted to Mulago hospital to map the mortality pattern, identify the risk factors for mortality and suggest potential interventions to reduce mortality. We also examined the difference in these factors among children HIV-infected severely malnourished children and those without HIV infection.

Methods

Study setting

Mulago Hospital, a national referral and teaching hospital, is situated in Kampala, the capital city of Uganda. The hospital provides various services ranging from primary to specialised care and serves urban, periurban and village populations from near and far districts. The Department of Paediatric and Child Health is one of the largest departments in the hospital, admitting over 10,000 children annually. The department has an Acute Care Unit which is open for admission 24 h a day. Admitted children are managed and observed for 24 h before being transferred to one of the four paediatric wards. Most of the children diagnosed with severe malnutrition are transferred to the Mwanamugimu Nutrition Unit either directly from the Acute Care Unit or the paediatric wards. This unit has two wards, a resuscitation ward with a bed capacity of 60 and a rehabilitation ward with a bed capacity of 25. The unit has been functional for nearly 4 decades. At the time of our study, the unit was supposed to use the Uganda national guidelines on management of severe malnutrition adapted from the WHO [18]. The national guideline includes optional measures in times of shortage or unavailability of supplies indicated in the WHO guidelines, such as: 1) high energy milk (100 Kcal/100 ml) made from fresh diary milk, vegetable oil and sugar, for use in place of F75 and F100; 2) standard WHO oral rehydration solution in the absence of ReSoMal; 3) use of multivitamin tablets in place of the combined mineral and vitamin mix. Copies of the national guidelines are usually made available to intern doctors and medical students.

Study design and subject selection

All children below the age of 60 months attending the department of Paediatrics and Child Health for acute illness between September 1 and November 15, 2003, were screened for severe malnutrition, using weight, height (or length for children less than 2 years) and presence of oedema. Measurements were taken in accordance with WHO standard techniques and compared with National Centre for Health Statistics (NCHS) reference population [19,20]. Severe malnutrition was defined as weight-for-height of <-3 z- score and/or presence of oedema (Figure 1). Children with length <49 cm were excluded from the study since the NCHS reference does not provide reference values for them. A total of 3,191 children were screened during the period. Of these, 236 (7.4%) were severely malnourished and their caregivers were informed of the study objectives and methods to be used, and requested for written consent to participate in the study. They were also counselled on having the HIV status of their children determined. Only children whose caregivers agreed to join the study by signing a consent form were enrolled.

A medical doctor trained in the study methodologies collected the children's demographic characteristics by interviewing the caregiver, filling in questionnaire, and determining their health characteristics using clinical history, physical examination and laboratory examinations of blood and urine specimens. A checklist was used to collect additional information from the patient's file immediately after the post-admission round by a team of doctors. Blood and urine specimens were drawn from each child whenever possible and the caregiver took the child for a chest x-ray examination.

The caregivers received pre-test and post-test counselling for HIV testing by a trained and experienced, mature multi-lingual counsellor. Caregivers of children who tested positive for HIV were counselled, and advised to attend the Paediatric Infectious Disease Clinic, a specialised outpatient clinic at the department for HIV positive children, for further management and subsequent follow-up. The clinic offers comprehensive HIV/AIDS care including free antiretroviral drugs. All other laboratory

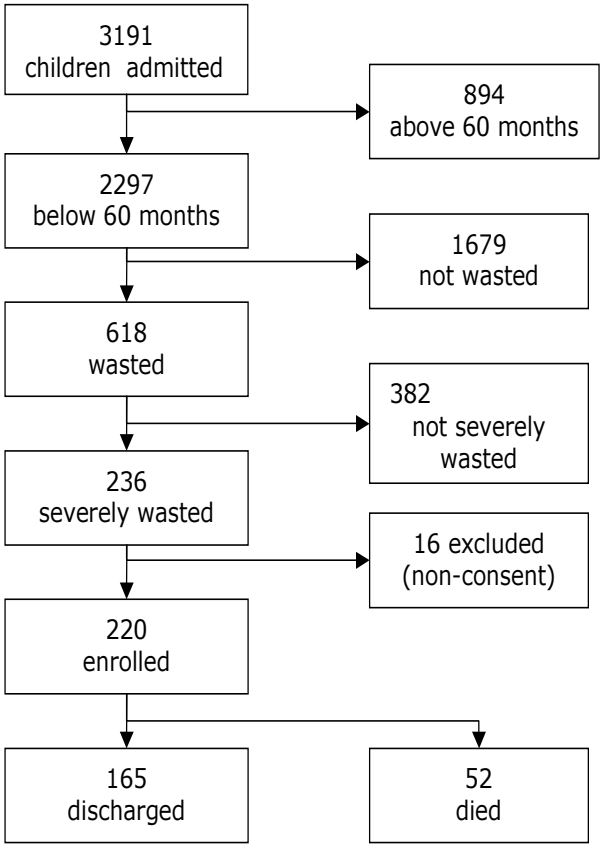

Figure 1
Study profile showing the process of enrolment of the 220 children with severe malnutrition below 60 months of age in Mulago hospital, Uganda, September – November 2003.

results were communicated to the caregivers and photocopies placed in the patients' files.

All enrolled children were followed-up daily, by an experienced study doctor on their respective wards who recorded the individual child's health development until outcome. Each child's daily management record was checked from files and recorded on observation forms, recording vital health signs, temperature, use of antibiotics, any fluids given and route of administration. Where necessary, the study provided any prescribed unavailable medication. Results of investigations were delivered to respective wards team promptly. Results needing urgent attention were communicated at once to the duty doctor.

Laboratory investigations

Biochemical tests

An automated chemistry Express plus 550 analyzer (Hema-screen 18, LIHD 169, S/N 802723, Italy) was used to analyse serum protein, potassium and serum sodium were analysed using flame photometry with automated flame photometers IL 943.

Haematological tests

Haematological tests were done within 6 h of specimen collection. Haemoglobin measurement was based on the cyan-methaemoglobin method [21], and white cell counts was performed according to principle of impedance or electrical resistance. Results were obtained from print-out and expressed as cells per cubic millimeter (cell/mm^3) and malaria parasites were examined from duplicate thick blood films from each specimen, using Field stain's, and examined under a microscope.

HIV Serology tests

Blood was taken in a 5 ml EDTA vacutainer tubes (Becton Dickinson, Franklin lakes, NJ USA) every morning between 8 – 11 am by venipuncture and transported within 4 h to Uganda Virus Research Institute (UVRI) laboratory, Entebbe, for serological testing. HIV testing was performed using standard HIV algorithm of two enzyme-linked immunoassays (EIA) in parallel. Western blotting, real-time polymerase chain reaction (RT-PCR) was performed to confirm a positive EIA test for children below the 18 months old and children with indeterminate results on EIA.

Blood and urine culture and sensitivity

Blood specimens for culture and sensitivity were cultured and sub-cultured on the blood agar, chocolate agar and crystal violet MacConkey agar plates and the plates incubated at 37°C for 24 h. The Kirby-Bauer diffusion method [22] was used to isolate, identify and characterize bacteria. Sensitivity to selected, commonly prescribed antibiotics were tested and graded as sensitive, intermediate or resistant.

Urine specimens with positive microscopic findings were cultured for bacterial sensitivity to commonly used antibiotics. Chest x-rays were taken to diagnose pneumonia, being reading and reported by a senior paediatric radiologist. The likely cause of death was determined by the research team based on clinical information, laboratory and x-ray findings. No Post-mortem examination was performed to verify the cause of death. We used clinical information, laboratory findings and x-ray reports to determine the likely cause of death.

Ethical considerations

The study was approved by the institutional review boards in Norway (REK VEST), Makerere Medical School, Mulago Hospital and the Uganda National Council for Science and Technology (UNCST).

Data Management

Raw data was cross-checked for completeness and correct labelling, and arranged in individual participants' fastened folders and stored securely in a filing cabinet. Data was entered and stored in Epidata http://www.epidata.dk. All data was stored securely in database accessible only to the research team. Stored data included patient identification inpatient or hospital number and study code. Anthropometric data was first analysed using the EPI-INFO version 6 and later exported to SPSS and subsequent descriptive and statistical analyses.

Statistical analysis

All statistical analyses were done using SPSS version 11.5. Univariate analysis by the Chi-squared test was used to measure association of each baseline characteristics with outcome, and logistic regression was used to explore the possibility of interactions. We conducted a multivariate analysis for all the variables using a hierarchical backward multiple regression to identify the variables most significantly associated with the outcome, and to adjust for the effects of age, sex and oedema (as dichotomous variables), as well as HIV status.

During modelling, variables were chosen according to their statistical significance of P <0.05, using odds ratio. Variables of clinical importance were included the initial model. Independent variables that persistently showed non-significant relationships with the dependent variable (death) during modelling were excluded from the final model. Age, HIV status and oedema were retained throughout modelling because of their primary interest in this study. We included interaction terms one at a time in the near final model and explored interactions within the multivariate model. We also conducted a survival function analysis for variables 'transfused', not 'transfused', as well as 'infused' and 'not infused'. Both unadjusted (Kaplan Meier) and adjusted (Cox) regressions were used.

Results

During the study period 3191 children were admitted to the paediatric wards, figure 1. Of these, 220 severely malnourished children of <60 months were enrolled. Their characteristics are summarized in Table 1. Over 50% of the children were in the age group 6–24 months with median and interquartile range of 16 months (IQR 13.5 – 23.5) and about half the children had oedema, with or without a weight-for-height of <-3 SD.

The mean haemoglobin level (Hb) was 8 g/dL (SE 2.2) and the range 2 – 14.6. Over 80% of the 217 children with haemoglobin results were anaemic, 14 (6.5%) were severely anaemic (Hb< 5 g/dL) and 8 were very severely anaemic (Hb <4 g/dL; Table 2).

Table 1: Characteristics of the 220 children below 60 months of age with severe malnutrition admitted to Mulago hospital, Uganda, September-November 2003

Age group	Male		Female		Total
Months	Oedema[a]	No oedema[b]	Oedema[a]	No oedema[b]	
0 – 5.9	0	2	1	3	6
6 – 11.9	14	13	7	9	43
12 – 23.9	38	37	20	26	121
24 – 35.9	8	7	5	6	26
36 – 47.9	5	2	3	3	13
48 – 59.9	3	2	4	2	11
Total	68	63	40	49	220

[a] Bilateral pedal oedema with or without a weight-for-height of <-3SD (z-score)

[b] Weight for height <-3 SD (z-score), but no bilateral pedal oedema.

Of the 220 children with severe malnutrition in hospital, 52 (24%) died, 107 (49%) were discharge against medical advice on achieving a target weight of 85% weight for height; and 59 (27%) self-discharged before target. The overall median duration from time of admission to time of death was 4 days (IQR 2 – 9), range 0 – 46 days. Fifteen children (29%) died in the first 48 h and 38 (73%) by the end of the first week (Figure 2).

A total of 52 (23.6%) children received blood transfusion during management, of which 24 died. The median Hb level of the children who died was 8 g/dL (IQR 6.5 – 10), range 2.7 – 14.3. The median time from transfusion to death was one day (IQR 0 – 3), range 0 – 19 days. Twenty (71%) of these children died within the first 48 h after transfusion (Figure 3). Likewise, 62 (28%) children received intravenous fluid during management, of which 26 died. The median time from time of infusion to death was 1 day (IQR 0 – 11), range 0 – 15 days. Twenty one (56.8%) of the deaths occurred within the first 48 h from the time of infusion (Figure 3).

The main causes included septicaemia (10) and severe pneumonia (8). Others were tuberculous meningitis (3), drug reactions (2), severe anaemia (2), hypothermia/ hypoglycaemia (2), hepatitis (1), cerebral malaria (1) and measles (1). For the rest of the children, fluid overload

Table 2: Distribution of haemogobin levels of 217 children below 60 months of age with severe malnutrition admitted to Mulago hospital, Uganda, September-November 2003

Haemoglobin levels (g/dL)	Number of children	Percentage (%)
< 4	8	4
4–4.9	6	3
5 – 8	92	42
8.1–10	94	43
>10	17	8
Total	217	100

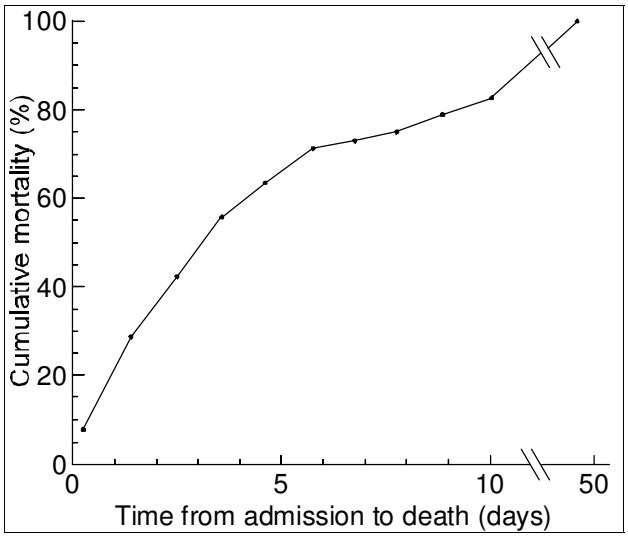

Figure 2
Cumulative mortality by time of death from admission of 52 deaths among 220 severely malnourished children in Mulago hospital, Uganda, September – November 2003.

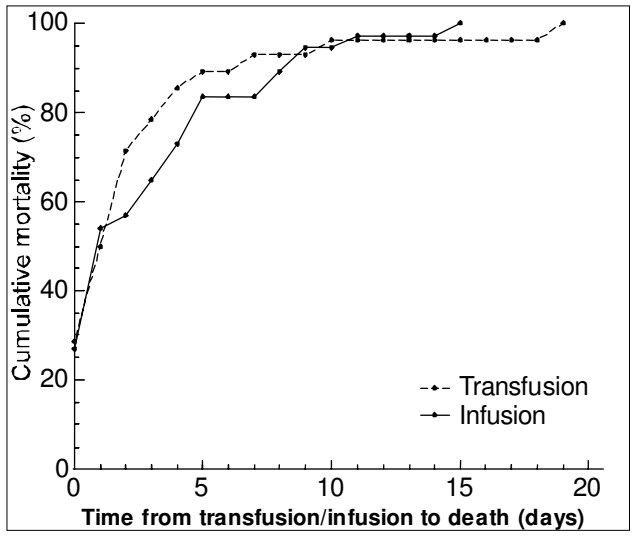

Figure 3
Cumulative mortality in the first week of admission of 28 and 37 children who were transfused and infused, respectively, by time from transfusion/infusion to death among severely malnourished children in Mulago hospital, Uganda, September – November 2003.

was the most likely cause. Of the 42 children who died in the first week, 17 (41%) tested positive for HIV-1 infection, 19 (45%) test negative HIV-1 infection and 6 (14%) had unknown HIV status. All the children were started on antibiotics at the time of admission. The majority were on a combination of ampicillin and gentamycin. Ten children were treated with ceftriaxone.

In the univariate analysis of the selected baseline and management characteristics, hypokalaemia, hypoalbuminaemia, transfusion intravenous fluid infusion were all associated with death (Table 3). There was no significant difference in mortality by sex, age-group (below 24 months or not), or by presence or absence of oedema.

The HIV positive children had a slight increase in the odds ratio for mortality but this was not significant (OR 1.8, 95% CI 0.93 – 3.5). None of the HIV infected children had been started on Antiretroviral (ARV) therapy during the study period. In the final multivariate model, we kept sex, age group, oedema and HIV status, all of which were still not significant. The 4 factors that were significant in the univariate analysis were serum potassium, serum albumin, transfusion and intravenous fluid infusion (Table 3). Blood transfusion and intravenous fluid infusion remained highly associated with death. We tested for all possible interactions in this final model and did not identify any that were significant.

We compared the risk of death in the two groups ('transfused' and 'not transfused') by survival analysis (Figure 4).

The adjusted relative risk of the fatality for transfusion comparing 'transfused' and 'not transfused' was 3.3 (95%, CI 1.84 – 6.0). Similarly, the adjusted relative risk of the

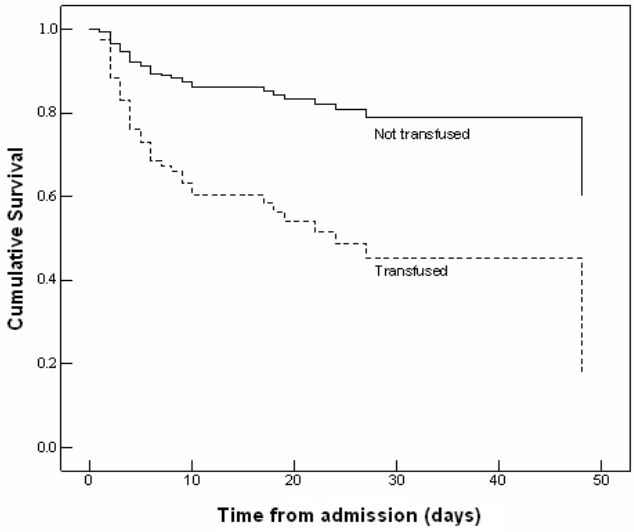

Figure 4
Cox regression survival curves of 194 severely malnourished children with complete data sets admitted to Mulago hospital, Uganda of which 52 died. The analysis was adjusted for the covariates retained in the final multivariate model (table 2) and stratified by transfusion status.

Table 3: Univariate and multivariate analysis of factors associated with death

	No of deaths/total (n = 220)	Unadjusted Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)
Sex			
Female	23/89	1	1
Male	29/131	0.8 (0.4 – 1.5)	1.0 (0.4 – 2.3)
Age group			
> 24 months	9/38	1	1
≤ 24 months	43/182	1.0 (0.4 – 2.3)	0.9 (0.3 – 2.4)
Oedema			
Absent	23/112	1	1
Present	29/108	1.4 (0.8 – 2.7)	2.0 (0.8 – 4.7)
Axillary temperature < 35°C			
No	44/169	1	
Yes	3/5	4.3 (0.7 – 26)	
Diarrhoea			
No	28/130	1	
Yes	24/90	1.4 (0.7 – 2.5)	
Blood glucose < 3 mmol/L)			
No	36/177	1	
Yes	7/18	2.5 (1.0 – 7.0)	
Serum K^+ < 3.5 mmol/L			
No	23/137	1	1
Yes	25/75	2.5 (1.0 – 4.8)*	2.4 (1.0 – 5.0)
Serum Na^+ < 135 mmol/L			
No	19/106	1	
Yes	29/106	1.7 (1.0 – 3.0)	
Hb < 5 g/dL			
No	46/203	1	
Yes	4/14	1.4 (0.4 – 4.6)	
Malaria parasites in blood			
No	45/186	1	
Yes	5/24	0.8 (0.3 – 2.3)	
Bacteria isolate in blood			
No	41/185		
Yes	10/32	1.6 (0.7 – 3.6)	
Total serum protein < 6 g/dL			
No	14/79	1	
Yes	34/133	1.6 (0.8 – 3.0)	
Serum albumin < 3.5 mg/dL			
No	3/42	1	1
Yes	45/170	4.7 (1.4 – 16)	4.3 (1.0 – 18)
HIV Status			
Negative	30/149	1	1
Positve	20/64	1.8 (0.9 – 3.5)	1.9 (0.8 – 4.4)
Blood transfusion			
No	28/142	1	1
Yes	24/52	3.5 (1.8 – 6.9)**	5.1 (2.2 – 12)***
Intravenous fluid infusion			
No	25/131	1	1
Yes	26/62	3.1 (1.6 – 6.0)*	4.8 (2.0 – 12)***

*p-value < 0.05; ***p-value < 0.001

fatality for infusion comparing 'infused' and 'not infused' was 2.2 (95%, CI 1.36 – 4.78; see Figure 5).

In order to evaluate whether the children who were transfused/infused were more seriously ill and more in need of a transfusion and or intravenous fluid infusion, we analysed circumstances leading to their transfusion/infusion. According to most guidelines blood transfusion in severely malnourished children is recommended only if Hb is <4 g/dL (very severe anaemia) or they are in a state of shock. In Table 4, a cross tabulation of these children with or without severe anaemia (Hb<5 g/dL) by their transfusion status and outcome is presented. Of the 180 children with Hb ≥ 5 g/dL, 44 were transfused. Of these,

Table 4: Outcome of 191 severely malnourished children with known haemoglobin concentrations on admission to Mulago hospital, Uganda, September-November 2003; categorised by their transfusion status and indication for transfusion [25]

	Transfusion may be indicated (<5 g/dL)	Transfusion not indicated (≥ 5 g/dL)	Total
Not transfused			
Died	2 (50%)	25 (18%)	27
Alive	2 (50%)	111 (82%)	113
Total not transfused	4 (100%)	136 (100%)	140
Transfused			
Died	2 (29%)	21 (48%)	23
Alive	5 (71%)	23 (52%)	28
Total transfused	7 (100%)	44 (100%)	51

Table 5: Outcome of 193 severely malnourished children with diarrhoea at admission to Mulago hospital, Uganda, September-November 2003; categorised by their infusion status and indication for infusion [25]

	Infusion may be indicated (Severe dehydration)	Infusion not indicated (No severe dehydration)	Total
Not infused			
Died	0 (0%)	25 (19%)	25
Alive	1 (100%)	105 (81%)	106
Total not infused	1 (100%)	130 (100%)	131
Infused			
Died	3 (33%)	23 (43%)	26
Alive	6 (67%)	30 (57%)	36
Total infused	9 (100%)	53 (100%)	62

21 (48%) died, mostly within the first week of admission (80%). Among the 136 children who had Hb ≥ 5 g/dL and were not transfused, only 25 (18%) died. The odds ratio for death in the transfused group was 4.8 (95% CI 1.5 – 7.2) compared to the untransfused.

Table 5 shows a similar a cross tabulation of the children with or without severe dehydration (WHO definition) by their infusion status and outcome. Of the 183 children with no severe dehydration, about 30% were infused. Of these, 23 (43%) died, mostly within the first week of admission (75%). The odds ratio for death in the infusion group was 3.1 (95% CI 1.6 – 4.3) compared to the not infused group.

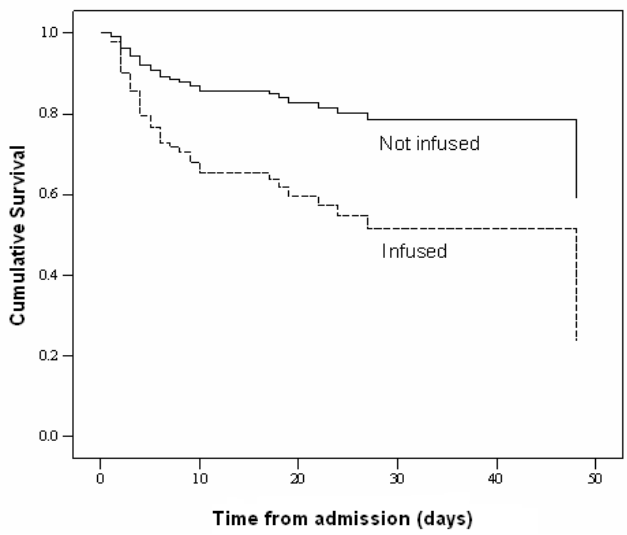

Figure 5
Cox regression survival curves of 194 severely malnourished children with complete data sets admitted to Mulago hospital, Uganda of which 52 died. The analysis was adjusted for the covariates retained in the final multivariate model (table 2) and stratified by infusion status.

Discussion

We have studied the risk factors for hospital death in 220 severely malnourished children below 60 months of age admitted to Mulago Hospital in Uganda, September – November 2003.

The main findings are that inappropriate use of transfusions and infusions seems to contribute significantly to case fatality. One third of the children were HIV positive but they did not have a statistically significant increased case fatality rate.

This study had several methodological advantages: 1) the use of reputable laboratories, especially for HIV detection at early age. 2) Combination of both clinical, laboratory and radiological assessments. 3) The consent to HIV testing was unexpectedly high (94%). 4) The analytical procedures used were adjusted for a number of possible confounders. There were, however, some drawbacks, such as the fact that children whose caregivers decided to leave hospital against medical advice were not followed up to determine their actual outcome. However, 50% of them left hospital after the first week of management. Another potential drawback is that all laboratory tests were performed once, on admission. Last, many caregivers did not take their children for x-ray examination.

Many of our results accord with previous findings in some African countries of high case fatality in hospitalized severely malnourished children [10-12,14,16,17,23]. Most deaths occurred in the first 7 days of admission. Irrespective of their HIV status, presence or absence of oedema, all severely malnourished children who received transfusion or intravenous fluid were at increased risk of dying compared to those who did not receive transfusion or intravenous infusion. Most of these deaths occurred soon after transfusion or/and infusion, within the first few days of admission. Therefore, fluid overload could be a plausible contributing factor to mortality. In addition, the survival experience of these children when transfused/

infused was less favourable than of those who were not transfused/infused at all, as previously reported [7,12,15]. This corroborates the general advice to restrict transfusions or infusions of severely malnourished children (20, 22). Children who had severe anaemia or severe dehydration were few compared to the cases of transfusion and intravenous fluid infusions (Tables 4 and 5). In Bangladesh, restriction of intravenous fluids in management of severe malnutrition in children with diarrhea highly contributed to the reduction of case fatality to < 5% (15). In this study, severely dehydrated children were infused with low sodium high potassium fluids at 20 ml/kg body weight for the first 2 h, then at 10 ml/kg body weight for the next. The rehydration was changed to rice-based oral rehydration solution given at 10 ml/kg body weight per h for 2 h, after which 5 ml/kg body weight per h for the next 10 h. Therefore, transfusion and infusion should only be given to severely malnourished children when genuinely needed, e.g. in cases of haemolytic anaemia or shock and given cautiously with close monitoring of vital signs for heart failure.

Although both the WHO and the Uganda national guidelines for management of severe malnutrition recommend withholding transfusion unless a severely malnourished child's haemoglobin level is <4 g/dl [20], and withholding intravenous infusion unless a child has signs of severe dehydration or is in shock, our study shows that these guidelines were not followed. There are several possible reasons for non-compliance which may include; the practical difficulty in diagnosing severe dehydration in a severely malnourished child and the lack of adequate and fully functioning laboratories. Often, a doctor has to base her/his decisions to transfuse on the presence of severe pallor. Yet, pallor in state of severe malnutrition can be exaggerated. Distinguishing a case of AIDS from severe malnutrition per se on clinical grounds can be difficult and lead to inappropriate management.

No adequate association between HIV positive status and death was found, as reported in other studies in Africa [14,16,17]. The effect of HIV on mortality among severely malnourished children might have been overshadowed by the prominent effect of fluid overload. Appropriate management of severe malnutrition may unveil the effect of HIV on mortality.

High prevalence of bacteraemia, urinary tract infection and pneumonia found in this study have also been reported elsewhere [10,24,25]. However, the lack of association between infections and death could possibly be attributed to the fact that all severely malnourished children admitted to this hospital are routinely treated with intravenous broad spectrum antibiotics and that other factors were strongly associated with death. Details of the bacterial isolates and antibiotic sensitivity are presented and discussed elsewhere[26]

Conclusion

The main risk factors for excess hospital deaths among severely malnourished children in Mulago hospital include blood transfusion and intravenous infusion. Any intervention to reduce deaths needs to focus on guideline compliance with respect to blood transfusions/infusions. This requires continued training of doctors and nurses in the paediatric wards in the management of severe malnutrition, especially where staff rotation (transfer) is common. Wide distribution and use of the WHO/national adapted version guidelines and user friendly job aids are advised.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

*A*ll authors participated in the design of the study, interpretation of the results, statistical analysis and writing the manuscript. HB supervised patient recruitment, follow-up and data collection. All authors read and approved the final manuscript.

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Paper II

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Reduction of unnecessary transfusion and intravenous fluids in severely malnourished children is not enough to reduce mortality

HANIFA BACHOU*§, JAMES K. TUMWINE*, ROBERT K. N. MWADIME†, TAHMEED AHMED & THORKILD TYLLESKAR‡§

**Department of Paediatrics & Child Health, School of Medicine and †FANTA/AED & Regional Centre for Quality Health Care, Makerere University, Kampala, Uganda, ‡Centre for Health and Population research (ICDDR,B), Dhaka, Bangladesh, and §Centre for International Health, University of Bergen, Norway*

Abstract

Aim: To test whether standardising the use of blood transfusions and intravenous (IV) infusions could reduce fatality in severely malnourished children admitted to Mulago Hospital, Kampala.

Methods: Improved adherence to the WHO protocol for blood transfusion and IV fluids was effected in patients with severe malnutrition by continuous medical education. A 'before and after' design was used to study 450 severely malnourished children (weight-for-height <-3 *Z*-score or presence of oedema) under 60 months of age. A total of 220 pre- and 230 post-'improved practice' patients were enrolled consecutively during the periods September to November 2003 and September to December 2004, respectively. Patients were followed up until discharge or death. The Kaplan–Meier survival curve and the Cox regression hazard model were used for univariate and multivariate analyses, respectively.

Results: Overall case fatality was 23.6% (52/220) in the pre-period and 24.8% (57/230) in the post-period ($p=0.78$). Most of the deaths occurred in the 1st week of admission (73%, 38/52 in the pre-period and 61%, 35/57 in the post-period) and were of children who had received blood transfusion or IV infusion or both in the pre-period. Mortality in children transfused and/or infused was significantly reduced in the post-period (82%, 31/38 in the pre-period *vs* 23%, 8/35 in the post-period, $p=0.008$). In the post-period, there was a significant reduction in the number of inappropriate blood transfusions (18%, 34/194 *vs* 3.5%, 8/230, $p=0.01$) and IV fluid infusions (27%, 52/194 *vs* 9%, 20/230, $p<0.001$). Survival improved in children who received blood transfusions in the post-period [hazards ratio (HR) 0.22, 95% CI 0.30–1.67 *vs* HR 4.80, 95% CI 1.71–13.51], as did that of children who received IV infusions (HR 2.10, 95% CI 0.84–5.23 *vs* HR 3.91, 95% CI 1.10–14.04).

Conclusion: Management according to the WHO protocol for severe malnutrition can reduce the need for blood and IV infusions. However, further studies are required to verify whether full implementation of the WHO protocol reduces the high case fatality in sub-Saharan hospitals.

Introduction

Hospital case-fatality rates for severe malnutrition remain high.[1–4] Poor-quality care, especially faulty case management, is considered to be the main cause.[3,5,6] WHO management guidelines include adequate and prompt triage, assessment and treatment.[7–9] Unfortunately, the financial and human resources required to implement the full WHO protocol and simultaneously address all aspects of management are unavailable in many low-resource settings.

Recently, we reported blood transfusions (BT) and intravenous (IV) fluid infusions to be major risk factors for mortality in severely malnourished children in Mulago Hospital.[10] This study was designed to

Reprint requests to: Dr Hanifa Bachou, Department of Paediatrics & Child Health, Medical School, Makerere University, PO Box 7072, Kampala, Uganda. Fax: +256 041 530324 / +47 55 97 4979; email: sab@utlonline.co.ug / hanifa.bachou@student.uib.no

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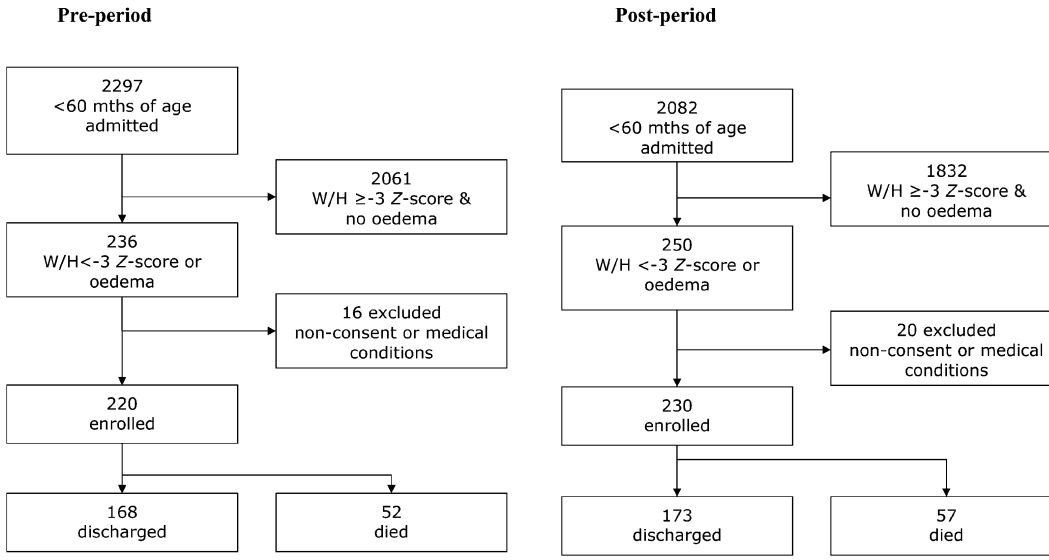

FIG. 1. Profile of the 450 severely malnourished children enrolled in the pre- and post-periods.

restrict the use of BT in children with very severe anaemia and to give IV infusions only to children with severe dehydration and shock with the aim of reducing mortality.

Subjects and Methods

The 'before and after' design[11] was used to study children <60 months of age admitted to Mulago Hospital, Kampala whose weight-for-height was <-3 *Z*-score of the United States National Center for Health Statistics median or who had bilateral pitting pedal oedema. The pre-period included children admitted to the paediatric wards between September and December 2003 before the introduction of the practice and the post-period included children admitted to the same paediatric wards between September and December 2004, 10 months after introduction of the improved practice (Fig. 1).

Improved practice to reduce unnecessary BT and IV infusions was in accordance with the WHO guidelines and included (i) BT for patients with haemoglobin (Hb) <4 g/dL or in septic shock with whole blood (not exceeding 10 ml/kg bodyweight and frusemide 1 mg/kg at the start of transfusion), (ii) patients with diarrhoea were given ReSoMal solution instead of standard WHO ORS, 5–10 ml/kg bodyweight every half hour for 2 hours then after every loose stool for up to 10 hours, alternating with F75 feeds; children who could not take oral feeds were given the solution by nasogastric tube (amount per kg bodyweight and frequency displayed on wall charts), (iii) restriction of IV fluids only to patients in shock (lethargic, unconscious with weak, fast pulse and cold hands) using either Ringers lactate (Na^+ 130 mmol/L, K^+ 5.4 mmol/L) or half-strength Darrow's (Na^+ 61 mmol/L, K^+ 17 mmol/L) plus 5% dextrose given at 15 ml/kg/h for 1 hour, then continued as for the regimen for treating dehydration. Doctors and nurses working in the paediatric wards and the nutrition unit received continuous medical education (CME) on the management of malnutrition. Supervision by the senior doctors and nurses was also strengthened.

F75 and F100 sachets were provided throughout the study period and given at 100 kcal/kg/day; feeds were given 3-hourly in phase 1 and the transition phase. Very sick children were fed 2-hourly by nasogastric

tube. These sachets replaced the high-energy milk used in the pre-period. Children with oedema received 100 kcal/kg/day and those with severe wasting were given 150 kcal/kg/day.

Other aspects of treatment remained the same. Systematic antibiotics were given parenterally for 7 days (ampicillin and gentamicin). Folic acid 5 mg daily and vitamin A were given as recommended by the national supplementation programme. Critical signs were recorded on each child's clinical monitoring form and included respiratory and pulse rates and temperature reading twice and weight once daily.

Children on BT or IV fluids were closely monitored in a side room where their respiratory and pulse rates were recorded every 30 minutes and clinical signs of fluid overload monitored (re-appearance or worsening of oedema and engorged jugular veins). For seriously ill children, serial weights were not taken because of the difficulty of using the hanging Salter scales. An increase in both respiratory and pulse rates, engorgement of the jugular veins or increasing oedema were a sign to stop IV fluids and re-assess the child for fluid overload.

Large feeding and rehydration charts were posted on the walls of the paediatric wards to aid correct selection of type, amount, route and period of administration of IV fluids. Copies of the guidelines were also distributed to all doctors and nurses and laboratory results were made available promptly to assist patient management.

Data collection

Details of the data collection have been published elsewhere.[10]

Ethical considerations

The study was approved by Makerere University Medical School, Mulago Hospital, the Uganda National Council for Science and Technology and the institutional review boards in Norway (REK VEST).

Statistical analysis

SPSS version 13 and STATA version 9 were used. Characteristics and health on admission were compared using the χ^2 test. Continuous parameters for cut-off points for normal levels were glucose <3 mmol/L, potassium <3.5 mmol/L, sodium <135 mmol/L, Hb <5 g/dL for severe anaemia, serum albumin <3.5 mg/dL and serum protein <5.5 mg/dL.

Kaplan–Meier curves were used to determine survival functions. Associations within and between groups were measured by univariate analysis using the log rank test. Cox's proportional hazards model was used to compare survival in the 1st week after BT or IV infusion with and without transfusion or with and without infusion adjusted for independent variables that were significant in univariate analysis in one of the two study periods and co-variates (sex and type of severe malnutrition). The median time from admission to first transfusion or infusion was 1 day [interquartile range (IQR) 0–3]. In children not receiving any transfusion or infusion, this median time of 1 day after admission was used as a starting point for the time variable in the regression. Failure was the death of a child. For both univariate and multivariate analyses, interactions between variables were not significant; we therefore present the models without these terms. A total of 98 and 184 cases with complete data were considered in the multivariate analysis in the pre- and post-periods, respectively.

Results

A total of 450 severely malnourished children <60 months of age were included in the study, 220 and 230 in the pre- and post-periods, respectively. The average median age of the children in the pre-period was

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TABLE 1. *Characteristics of patients with severe malnutrition admitted in the pre- and post-periods.*

	Pre-period *n*/total (%)	Post-period *n*/total (%)
Male	131/220 (59)	150/230 (65)
Age ⩽24 mths	182/220 (83)	175/230 (76)
Oedema⋆	108/220 (49)	144/230 (63)
Diarrhoea	88/220 (40)	96/230 (42)
Severe dehydration†	12/220 (6)	32/230 (14)
Hypothermia[a]	5/174 (3)	19/225 (8)
Respiratory tract infection[b]	132/166 (79)	144/206 (70)
Bacteraemia	31/217 (14)	45/228 (20)
HIV-1-positive†	64/213 (30)	86/199 (43)
Malaria[c]	18/214 (8)	18/230 (8)
Hypoglycaemia[d†]	18/195 (9)	5/213 (2)
Hypokalaemia[e†]	75/212 (35)	103/218 (45)
Hyponatraemia[f⋆]	106/212 (64)	149/217 (50)
Severe anaemia[g]	14/217 (6)	19/230 (8)
Hypoproteinaemia[h]	133/212 (63)	147/218 (63)
Hypo-albuminaemia[i]	170/212 (80)	199/218 (86)

[a] Hypothermia, axillary temperature <35°C; [b] respiratory infection, diagnosed by chest radiograph; [c] malaria, blood slide positive for malaria parasites; [d] hypoglycaemia, blood glucose <3 mmol/L; [e] hypokalaemia, K^+ <3.5 mmol/L; [f] hyponatraemia, Na^+ <135 mmol/L; [g] severe anaemia, Hb <5 mg/dL); [h] hypoproteinaemia, serum protein <5.5 g/dL; [i] hypo-albuminaemia, serum albumin <3.5 g/dL. Significant difference: ⋆ $p<0.001$, † $p<0.05$.

16 months (IQR 12–24) and 18 months (IQR 13–24) in the post-period. Distribution by age and gender was similar in both periods. There were six children <6 months of age in each period. There were significantly more cases of oedematous malnutrition, severe dehydration, hypothermia, HIV infection and hypokalaemia and fewer of hypoglycaemia in the post-period than in the pre-period (Table 1). The median (IQR) duration of admission until death was similar in both periods [4 (2–9) and 5 (3–13) days] and also the duration of admission until self-discharge [8 (5–13) and 8 (3–17) days]. However, the duration of admission until formal discharge was significantly longer in the post-period [13 days (5–23)] than in the pre-period [8 days (4–19), $p=0.004$].

Case fatality

Overall case fatality was 23.6% (52/220) in the pre-period and 24.8% (57/230) in the post-period ($p=0.78$). Over 70% (38/52) of deaths in the pre-period and 61% (35/57) in the post-period occurred in the 1st week of admission (Table 2). Most early deaths in the pre-period were children who had received either BT or IV infusions or both (82%, 31/38) but significantly fewer deaths were associated with this in the post-period (23%, 8/35, $p=0.008$).

TABLE 2. *Number of patients who died in the 1st week of admission by BT and IV infusion status.*

Died in 1st week	Pre-period *n* (%)	Post-period *n* (%)	Total *n* (%)
Transfusion	12/38 (31.6)	5/35 (14.3)	17/73 (23.3)
Infusion	12/38 (31.6)	3/35 (8.6)	15/73 (20.5)
Both	7/38 (18.4)	0/35 (0)	7/73 (9.6)
Neither⋆	7/38 (18.4)	27/35 (77.1)	34/73 (73.0)
Total	38/38 (100)	35/35 (100)	73/73 (100)

⋆ Neither transfused nor infused

Blood transfusion and anaemia

The proportion of children who received IV fluids (BT and IV infusion) fell from 27% (52/194) to 9% (20/230) ($p<0.001$) and the number of children who received BT in the 1st week of admission also fell, from 18% (34/194) in the pre-period to 3.5% (8/230) in the post-period ($p=0.01$).

Patients were compared with regard to requirement for BT and outcome in the 1st week of admission in the two periods. The majority (44/51) of those who received BT in the pre-period did not have severe anaemia (Hb ⩾5 g/dL) and 39% of them died. As this practice declined, so did the associated mortality (Table 3). However, the likelihood of receiving transfusion also decreased in the group with very severe anaemia. In spite of this, mortality in this group also declined (Fig. 2).

By both univariate and multivariate analysis of the pre-period, BT was associated with significantly poorer survival (HR 3.20, 95% CI 1.74–5.86 and HR 4.80, 95% CI 1.71–13.51, respectively). In the post-period, however, BT was associated with improved survival (HR 0.83, 95% CI 0.26–2.69 and HR 0.22, 95% CI 0.30–1.67) (Tables 4 & 5).

IV fluid infusion and dehydration

The proportion of children who received IV infusions in the pre-period was 32% (62/193) and was significantly less in the post-period (15%, 35/230, $p<0.001$). However, >50% of the IV infusions were administered in the 1st week of admission in both periods, 60% (37/62) and 51% (18/35), respectively.

Twenty-eight per cent (53/184) of the children who were not severely dehydrated in the 1st week of admission received IV infusion in the pre period, irrespective of dehydration status, and 30% (16/53) died. As this practice decreased (27/214), so did the associated mortality (1/27) in the post-period (Table 6). However, the number of severely dehydrated children who were not infused increased slightly and their survival also declined. In addition, survival of those who received IV fluids in the 1st week did not improve much (Fig. 3).

IV infusions contributed significantly to lower survival in both univariate (HR 2.54, 95% CI 1.39–4.66) and multivariate analysis (HR 3.91, 95% CI 1.10–14.04). In the post-period, the contribution of IV infusion to poorer survival was not significant by either univariate (HR 21.54, 95% CI 0.71–3.32) or multivariate analysis (HR 2.10, 95% CI 0.84–5.23).

HIV/AIDS infection

Thirty per cent (64/213) of the children were infected with the HIV-1 virus in the pre-period and 43% (89/199) in the

TABLE 3. *Number of patients who died in the 1st week of admission by anaemia and BT status.*

	Pre-period *n*/total (%)	Post-period *n*/total (%)
Very severe anaemia (Hb <4 g/dL)		
Transfused	0/4 (0)	0/1 (0)
Not transfused	1/2 (50)	0/7 (0)
Severe anaemia (Hb 4–<5 g/dL)		
Transfused	1/3 (33)	0
Not transfused	1/2 (50)	3/11 (27)
No severe anaemia (Hb ⩾5 g/dL)		
Transfused	17/44 (39)	3/19 (16)
Not transfused	16/136 (12)	28/188 (15)
Total	36/191 (19)	34/226 (15)

All the numbers in the table are of patients with known haemoglobin and transfusion status.

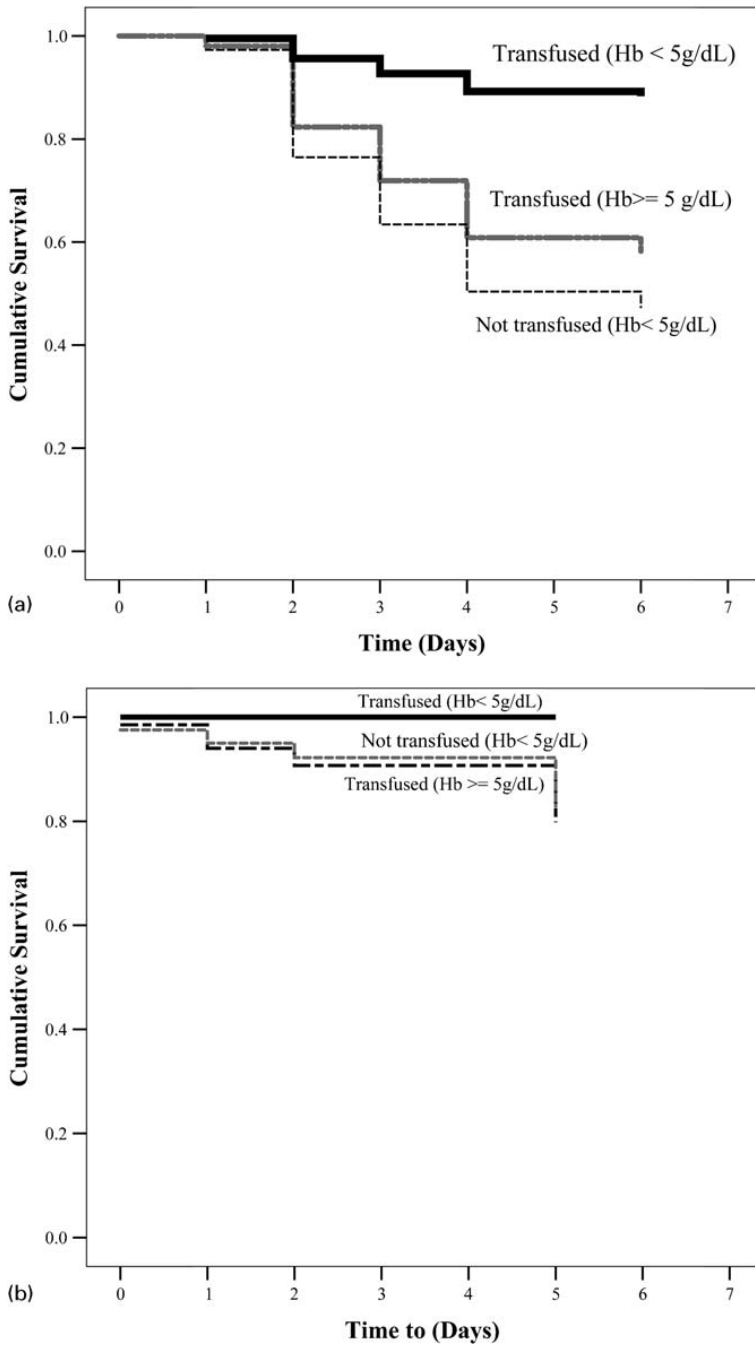

FIG. 2. Cox proportional survival regression curves showing unadjusted cumulative survival of patients 1 week after BT or IV infusion by transfusion status in the pre- (2a) and post-periods (2b).

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TABLE 4. *Univariate Cox regression analysis of selected factors, fluid management and death 1 week after transfusion or infusion**.

	Pre-period		Post-period	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Male	0.84 (0.45–1.55)	0.575	0.63 (0.34–1.15)	0.132
Oedema	1.29 (0.70–2.38)	0.410	0.95 (0.51–1.78)	0.879
Diarrhoea	1.41 (0.77–2.59)	0.264	1.67 (0.92–3.04)	0.094
Respiratory infection	0.39 (0.17–0.88)	**0.023**	1.34 (0.66–2.73)	0.410
Bacteraemia	1.76 (0.84–3.69)	0.134	1.30 (0.64–2.64)	0.474
Bacteriuria	1.77 (0.80–3.90)	0.156	0.76 (0.30–1.94)	0.563
HIV-1 status	1.63 (0.87–3.07)	0.129	1.32 (0.71–2.44)	0.372
Hypothermia	2.67 (0.82–8.70)	0.103	1.09 (0.38–3.02)	0.884
Hypoglycaemia	2.57 (1.12–5.90)	0.025	3.98 (1.22–12.97)	0.022
Hypokalaemia	1.54 (0.83–2.88)	0.172	0.77 (0.42–1.43)	0.416
Hyponatraemia	1.35 (0.72–2.53)	0.343	0.94 (0.50–1.77)	0.861
Severe anaemia	1.79 (0.64–5.04)	0.269	1.21 (0.43–3.8)	0.721
Blood transfusion	3.20 (1.74–5.86)	**<0.001**	0.83 (0.26–2.69)	0.752
IV fluid infusion	2.54 (1.39–4.66)	**0.003**	1.54 (0.71–3.32)	0.271

* Starting point for the time variable was 1 day after admission.

TABLE 5. *Multivariate Cox regression analysis of selected factors, fluid management and death 1 week after transfusion or infusion**.

	Pre-period		Post-period	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Male	0.86 (0.29–2.55)	0.79	0.60 (0.30–1.19)	0.15
Oedema	1.98 (0.58–6.78)	0.28	0.93 (0.41–2.01)	0.86
Diarrhoea	0.57 (0.17–1.85)	0.35	1.54 (0.78–3.03)	0.21
Hypothermia	2.18 (0.41–11.41)	0.36	0.94 (0.28–3.14)	0.93
Respiratory infection	0.37 (0.19–1.19)	0.10	1.26 (0.55–2.87)	0.58
Bacteraemia	3.1 (0.93–10.26)	0.07	1.69 (0.77–3.71)	0.19
Hypoglycaemia	0.53 (0.08–3.33)	0.52	5.35 (1.32–21.60)	0.02
Hypokalaemia	1.73 (0.64–4.70)	0.28	0.57 (0.27–1.20)	0.14
HIV-1-positive	1.31 (0.43–3.95)	0.63	0.89 (0.44–1.82)	0.76
Blood transfusion	4.80 (1.71–13.51)	**0.003**	0.22 (0.03–1.67)	0.14
IV fluid infusion	3.91 (1.10–14.04)	**0.04**	2.10 (0.84–5.23)	0.11

* Starting point for the time variable was 1 day after admission.

TABLE 6. *Number who died in the 1st week of admission by dehydration status.*

	Pre-period *n*/total (%)	Post-period *n*/total (%)
Severe dehydration		
IV-infused	3/9 (33)	1/8 (12)
Not IV-infused	0/1 (0)	4/8 (50)
No severe dehydration		
IV-infused	16/53 (30)	1/27 (4)
Not IV-infused	19/131 (14)	26/187 (14)
Total	38/194 (20)	32/230 (14)

Includes only children with known dehydration and IV infusion status.

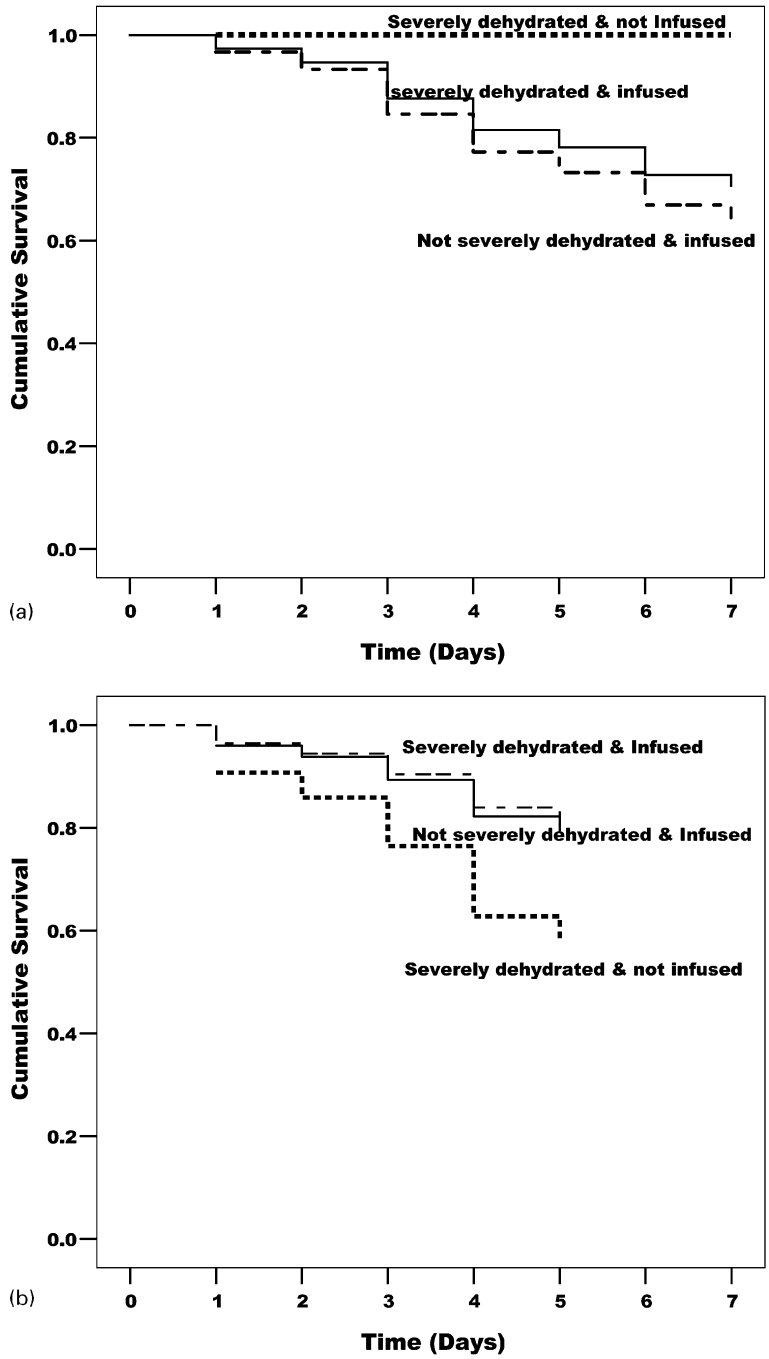

FIG. 3. Cox proportional survival regression curves showing unadjusted cumulative survival of patients 1 week after BT or IV fluids by intravenous fluid infusion status in the pre- (3a) and post-periods (3b).

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post-period. In both periods. however, HIV-1 infection was not a significant factor in mortality in the 1st week of admission by univariate and multivariate analysis (Tables 4 and 5).

Discussion

This and the previous study demonstrate that BT and IV infusions are important contributors to mortality in severely malnourished children.[10] They also demonstrate that severely malnourished children need extremely precise protocol management. There was a significant decrease in the number who received BT and IV infusions in children admitted in the post-period and the deaths associated with this mode of care declined significantly in the 1st week of admission. However, overall case fatality did not decrease (23.6% *vs* 24.8%), in contrast with a similar study in Bangladesh where the case fatality decreased from 47% to <5%.[12] Although such low fatality rates have been achieved/reported elsewhere,[12–15] they have not yet been reported in hospital settings in the sub-Saharan region.[5,16,17]

The reasons for the lack of an overall decline in case fatality despite improvement in practices for BT and IV infusions need to be explored. There were some differences between the pre- and post-period groups. Patients in the post-period had more severe dehydration, hypoglycaemia, hyponatraemia and hypokalaemia and a higher prevalence of oedema (Table 1). However, these differences between the groups are probably not sufficiently large to entirely explain the non-effect of the improved practice.

One particular factor that differed between the two periods was the number of patients with HIV infections (30% *vs* 43% in the pre- and post-periods, respectively). HIV-1 infection has increased the burden of disease in children[18,19] and led to an increase in paediatric admissions in sub-Saharan Africa along with the associated high mortality.[20–24] In Malawi, HIV-1 infection is a major contributor to mortality in severely malnourished children.[25] In this study, the proportion of severely malnourished, HIV-1-infected children and their mortality rate were similar to reports from elsewhere in the region.[21,25–27] The increase in children admitted with HIV infection probably reflects improved care in the community, including better accessibility to admission. This might be partly owing to the new paediatric infectious disease clinic in Mulago Hospital which identifies a greater number of HIV-infected children and refers them for admission when seriously ill. In our analysis, however, the increased prevalence of HIV in the study children did not seem to have contributed significantly to case fatality in the 1st week.

Another possible explanation is the role of infection and metabolic derangement. Infections are reported to be the main contributor to the continuously high case fatality rates in severely malnourished children in sub-Saharan Africa. A study in Tanzania demonstrated a high incidence of nosocomial bacterial infections in hospitalised, severely malnourished children and suggested that this could be the main cause of mortality.[28] However, most deaths in both study periods occurred in the 1st week of admission, limiting the influence of nosocomial bacterial infections. Late care-seeking is another factor. In Uganda, although awareness of childhood illnesses is high, care-seeking remains low. Less than 20% of mothers contact health facilities as the first care option.[29] Children present late, often in a critical condition.[30] If late arrival is coupled with inadequate triage on admission, the survival of severely malnourished children can be jeopardised, in spite of somewhat improved management. In this study, the children in the post-period were more sick and more immunocompromised than those in the pre-period on admission and presented with more complications

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such as severe dehydration, hypothermia and hypokalaemia.

Improved practice regarding BT and IV infusions in the management of severe malnutrition was effective in reducing deaths associated with transfusion and infusion. However, it did not reduce overall case fatality. Perhaps, in this setting, the potential causes of mortality are so many that controlling only one merely shifts the mortality to other causes. Full implementation of the WHO protocol or locally adapted similar protocols with adequate financial and human resources might have a greater impact on overall case fatality.

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Paper III

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Research

Severe malnutrition with and without HIV-1 infection in hospitalised children in Kampala, Uganda: differences in clinical features, haematological findings and CD4+ cell counts

Hanifa Bachou*[1,2], Thorkild Tylleskär[2], Robert Downing[3] and James K Tumwine[1]

Address: [1]Department of Paediatrics and Child Health, Makerere University Medical School, P O Box 7072, Kampala, Uganda, [2]Centre for International Health, University of Bergen, Norway and [3]CDC/Uganda Virus Research Institute Research Collaboration, P O Box 49, Entebbe, Uganda

Email: Hanifa Bachou* - hanifa.bachou@student.uib.no; Thorkild Tylleskär - thorkild.tylleskar@cih.uib.no; Robert Downing - rqd6@CDC.gov; James K Tumwine - jtumwine@imul.com

* Corresponding author

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Abstract

Background: The aim of this study was to describe the clinical features, haematological findings and CD4+ and CD8+ cell counts of severely malnourished children in relation to human immunodeficiency virus (HIV) infection.

Methods: The study was conducted in the paediatric wards of Mulago hospital, which is Uganda's national referral and teaching hospital. We studied 315 severely malnourished children (presence of oedema and/or weight-for-height: z-score < -3) and have presented our findings. At admission, the CD4+ and CD8+ cells were measured by the flow cytometry and HIV serology was confirmed by Enzyme linked Immunoassay for children >18 months of age, and RNA PCR was performed for those ≤18 months. Complete blood count, including differential counts, was determined using a Beckman Coulter counter.

Results: Among the 315 children, 119 (38%) were female; the median age of these children was 17 months (Interquartile range 12–24 months), and no difference was observed in the HIV status with regard to gender or age. The children showed a high prevalence of infections: pneumonia (68%), diarrhoea (38%), urinary tract infection (26%) and bacteraemia (18%), with no significant difference with regard to the HIV status (HIV-positive versus HIV-negative children). However, the HIV-positive children were more likely to have persistent diarrhoea than the HIV-uninfected severely malnourished children (odds ratio (OR) 2.0, 95% confidence interval (CI) 1.2–3.6). When compared with the HIV-negative children, the HIV-positive children showed a significantly lower median white blood cell count (10700 versus 8700) and lymphocyte count (4033 versus 2687). The CD4+ cell percentages were more likely to be lower in children with non-oedematous malnutrition than in those with oedematous malnutrition even after controlling for the HIV infection.

The novel observation of this study is that the CD4+ percentages in both HIV-positive and HIV-negative children without oedema were lower that those in children with oedema. These observations appear to imply that the development of oedema requires a certain degree of immunocompetence, which is an interesting clue to the pathophysiology of oedema in severe malnutrition.

Background

Severe malnutrition has been associated with acquired immunodeficiency (AID) among children worldwide, and it is referred to as Nutritionally Acquired Immunodeficiency Syndrome or NAIDS [1,2]. With the advent of the human immunodeficiency virus (HIV) pandemic, there has been a tendency to overlook the role of malnutrition in immunodeficiency, and indeed, only a handful of studies have investigated the $CD4^+$ and $CD8^+$ lymphocyte subsets in severely malnourished children [3,4].

There is little information on the effect of the added burden of HIV infection on the clinical features [5-7] and cellular immunity of severely malnourished children. The objective of this study was to report the clinical features, haematological findings and $CD4^+$ and $CD8^+$ lymphocyte subsets of severely malnourished children with regard to their HIV status.

Subjects and methods

All severely malnourished children consecutively admitted to the paediatric wards of Mulago hospital, which is Uganda's national referral and teaching hospital, during the two peak seasons of malnutrition, namely, September-November 2003 and September-December 2004 were followed up from the time of admission to outcome (death or discharge). In this study, we included a total of 450 severely malnourished children (presence of oedema and/or weight-for-height: z-score < -3) after obtaining the informed consent of their parents or caregivers (Figure 1); the age of these children was below 60 months. The risk factors for death in the first peak (2003) have been stated in a previous report that describes the methodology in greater detail.

In this paper, we report the complete results of the HIV tests as well as the $CD4^+$ and $CD8^+$ cell counts and percentages of the 315 children. In the case of 135 children, complete laboratory data could not be obtained; this was due to the lack of reagents in the case of 89 children; inadequate blood volume in 38, haemolysis in 6 and absence of blood sample in 2. The basic characteristics of the 315 children with complete results were compared with those of the 135 children with incomplete results.

The following parameters were recorded for all the children: demographic characteristics (age and sex), clinical features (weight, height/length and presence of oedema and diarrhoea), haematological tests (haemoglobin concentration, white blood cell (WBC) count and differentials and presence of malarial parasites), HIV tests (ELISA and RNA PCR), microbial tests (blood and urine culture and sensitivity), immunologic tests ($CD4^+$ and $CD8^+$ cell counts and percentages) and chest x-ray reports. We used the $CD4^+$ cell percentage to categorize children with or without the HIV infection. The clinical definition of malnourishment classified all our patients into category C because all the children were severely malnourished. The haemoglobin concentrations were evaluated according to the WHO criteria: <5 g/dL and <4 mg/dL are referred to as severe anaemia and very severe anaemia, respectively.

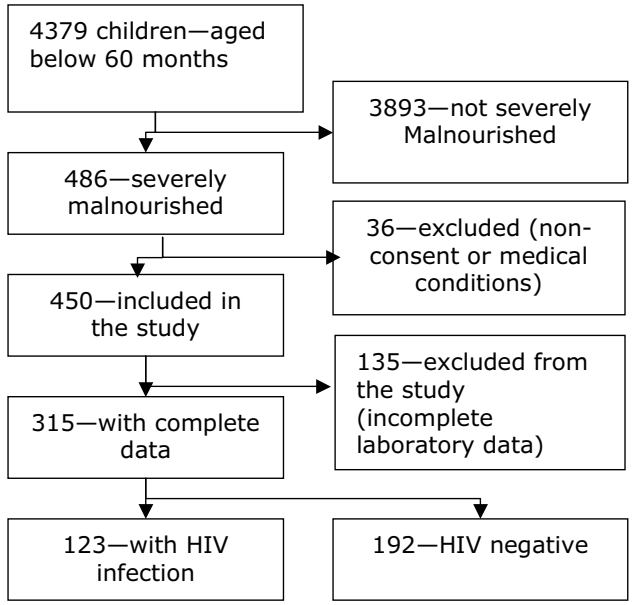

Figure 1
Study profile showing the enrolment process of the 315 children in the study.

Laboratory methods

Blood was collected in 5-ml EDTA vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA) in the mornings between 8–11 am by venipuncture and transported within 4 h to Uganda Virus Research Institute (UVRI) laboratory, Entebbe for serological testing. HIV testing was performed using the standard HIV algorithm of two enzyme-linked immunoassays (EIA) in parallel. Western blot and real-time polymerase chain reaction (RT-PCR) were performed to confirm a positive EIA test for children below 18 months of age and those with indeterminate results on EIA.

TriTEST reagents (CD3, FITC/CD4, PE/CD45, PerCP and CD3, FITC/CD8, PE/CD45, Per CP) were used to stain PBMC for $CD4^+$/$CD8^+$ cell counting according to the manufacturer's instructions. FACScan instrument and MultiSET software were used to perform flow cytometry and report the absolute $CD4^+$ and $CD8^+$ cell counts of each sample by using the dual-platform approach (Becton Dickinson, Franklin Lakes, NJ, USA). Complete blood count, including differential counts, was assessed using a

Beckman Coulter counter [8]. Blood was stained within 12 h of collection, and the observations were analysed within 24 h.

Severe malnutrition was defined according to the WHO classification and the presence of severe wasting (weight-for-height < 3 SD of the NCHS/WHO reference values with no oedema) and/or oedematous malnutrition (presence of symmetrical oedema involving at least the feet) [9]. The children were divided in two groups; HIV-positive and HIV-negative groups.

The study protocol was approved by the Regional Committee for Medical Ethics, Bergen, Norway (REK Vest), Makerere University Faculty of Medicine Ethics and Research Committee, Mulago Hospital Ethics Committee and the Uganda National Council for Science and Technology.

Statistical analysis was performed using SPSS version 13. Medians were used to calculate the central tendency and interquartile range (IQR) for the spread of haemoglobin concentration, WBC, total lymphocyte and $CD4^+$ and $CD8^+$ cell counts. Children were grouped by their gender (male or female), age in months (≤24 months and >24 months), presence or absence of oedematous malnutrition and HIV infection and $CD4^+$ levels ($CD4^+$ cell percentage < 20% and < 15%). Chi square and Wilcoxon-Mann-Whitney tests and multivariate analysis were used to determine differences with regard to the HIV status, gender and type of severe malnutrition (oedematous versus non-oedematous). A 2-tailed p value of < 0.05 was considered significant. Binary logistic regression models were constructed using the HIV status as the outcome variable. The appropriate important baseline data of clinical significance was included in a regression model and used for adjustment. The chi-square test was used to select variables according to their statistical significance ($p < 0.05$). Dummy variables were created for the categorical variables used. The chosen dependent variables were tested for interactions, and the very significant variables were stratified to assess for the possibility of effect modification. Positive interactions remained in the final model. Independent variables that showed a persistently non-significant relationship with the dependant variable during modelling were excluded from the final model.

Results

Of the 315 children, 119 (38%) were female, and the median age of these children was 17.0 months (IQR 12–24). The age of half the children was between 12–24 months, and that of a few children (3%) was below 6 months (Table 1). The age distribution was not affected by their HIV status. Almost half the children (170/315) had oedematous malnutrition (kwashiorkor and marasmic-kwashiorkor). These characteristics (sex, age and type of malnutrition) were comparable to those of the 135 children with incomplete laboratory data.

HIV infection was detected in 123/315 children (approximately 40%). The HIV-infected children were less likely to present with oedema (OR 0.5, 95% CI 0.3–0.7). Of all the severely malnourished children, only 27 (9%) had no identifiable infection on admission, 51 (16%) had only one type of infection and the majority, that is, 227 (72%) had more than one type of infection on admission. The infections included pneumonia (68%), diarrhoea (38%), urinary tract infection (26%), bacteraemia (18%), malaria (9%) and oral thrush (11%) (Table 2). Overall, there was no significant difference in the prevalence of infection with regard to the HIV status. However, the HIV-1-infected children were more likely to have persistent diarrhoea and oral thrush (Table 2).

The median haemoglobin concentration of these children was below 9 g/dL. There was no significant difference in the haemoglobin concentration with regard to the type of severe malnutrition or HIV status (Table 3). The total WBC count was significantly lower in the HIV-positive children (8.9×10^6; IQR 5.4–11.3) than in the HIV-negative children (9.1×10^6; 7.2-3.5) ($p = 0.028$). Among the HIV-infected children, the total WBC count was lower in the non-oedematous children than in the oedematous

Table 1: Characteristics of children aged below 60 months with severe malnutrition during 2 peak malnutrition periods.

Age group	HIV-positive children n = 123		HIV-uninfected children n = 192		Total
Months	Male	Female	Male	Female	
0–5.9	1	2	4	4	11
6–11.9	15	8	21	14	58
12–23.9	36	21	66	37	160
24–35.9	17	8	19	6	50
36–47.9	4	4	6	6	20
48–59.9	2	5	5	4	16
Total	75	48	121	71	315

Table 2: Characteristics, co-existing medical conditions and diagnosis of children aged <60 months with severe malnutrition.

	HIV-positive children n (%)	HIV-negative children n (%)	Odds ratio (95% CI)
Symptoms and signs	**(n = 123)**	**(n = 192)**	
Diarrhoea (all)	52 (42)	67 (35)	1.4 (0.9–2.2)
Persistent diarrhoea (>2 weeks)	32 (26)	28 (15)	2.1 (1.1–3.8)*
Oral thrush	20 (16)	15 (8)	2.3 (1.1–4.7)*
Bilateral oedema (nutritional)	53 (43)	119 (62)	0.5 (0.3–0.7)*
Severe dehydration	7 (6)	11 (6)	1.0 (0.4–2.7)
Chest x-ray findings	**(n = 109)**	**(n = 158)**	
Bronchopneumonia	26 (24)	48 (30)	0.7 (0.4–1.3)
Interstitial pneumonia	40 (37)	48 (30)	1.3 (0.8–2.2)
Suspected tuberculosis	14 (13)	18 (11)	1.2 (0.5–2.4)
Blood tests	**(n = 122)**	**(n = 191)**	
Malarial parasites	10 (9)	19 (11)	0.9 (0.4–1.9)
Severe anaemia (Hb < 5 g/dL)	10 (8)	2 (6)	1.3 (0.6–3.3)
Bacteraemia	24 (20)	32 (17)	1.2 (0.7–2.2)
Urine tests	**(n = 109)**	**(n = 160)**	
Bacteruria	33 (30)	36 (23)	1.5 (0.9–2.6)

*Statistically significant

children. However, this difference was not observed among the HIV-uninfected children (Table 4).

The total lymphocyte counts were 2.9×10^9 (IQR 2.0–4.9) in the HIV-positive children and 4.5×10^9 (IQR 2.9–6.3) in the HIV-uninfected children ($p = 0.008$). The absolute lymphocyte counts were 2.7×10^9 (IQR 1.8–4.9) in the HIV-infected children and 4.0×10^9 (2.8–5.6) in the HIV-uninfected children ($p < 0.001$). The total lymphocyte, monocyte and neutrophil counts were lower in the HIV-positive children with no oedema than in those with oedema; this was not observed among the HIV-negative children.

Regardless of their HIV status, children with severe non-oedematous malnutrition (marasmus) had significantly lower $CD4^+$ count, $CD4^+$and $CD8^+$ percentages and $CD4^+$/$CD8^+$ ratios than those with oedematous malnutrition (kwashiorkor and marasmic-kwashiorkor) (Table 4 and Figure 2)

The $CD4^+$ cell percentage was below 25% in one-third of the 315 severely malnourished children. Among these one-third children, the $CD4^+$ cell percentage was between 15%–24% in 17% (55/315) children, indicating moderate cellular immunosuppression, while it was below 15% in 18% children, indicating severe cellular immunosuppression. Both these categories of cellular immunosuppression were present in HIV-infected and HIV-uninfected groups (Table 5). The $CD4^+$ cell percentages were more likely to be below 15% (OR 4.2, CI 1.4–12.6) and between 15%–25% (OR 2.0, CI 0.6 – 6.8) in children with

Table 3: Laboratory data of all severely malnourished children aged <60 months grouped by their HIV status.

	HIV-positive median (IQR) n = 123	HIV-negative median (IQR) n = 192
Haemoglobin	7.8 (6.4–9.2)	8.1 (6.5–9.6)
Total WBC (10^9/L)	8.9 (5.4–11.3)	9.1 (7.2–13.5)**
Neutrophils (10^9/L)	4.9 (2.8–8.0)	5.9 (3.4–8.9)
Neutrophils (%)	59 (35–71)	55 (41–65)
Monocytes (10^9/L)	0.22 (0.11–0.94)	0.28 (0.15–0.53)
Monocytes (%)	2 (1.8–7.5)	2 (1.8–5)
Total lymphocytes (10^9/L)	2.9 (2.1–4.9)	4.5 (2.9–6.3)**
Lymphocytes (%)	39 (26–50)	40 (32–50)
$CD4^+$ cell count (10^6/L)	497 (280–1379)	1265 (829–1758)***
$CD4^+$ cells (%)	18 (12–34)	33 (26–40)***
$CD8^+$ cell count (10^6/L)	880 (490–1750)	588 (331–913)***
$CD8^+$ cells (%)	31 (23–50)	15 (13–21)***
$CD4^+$/$CD8^+$ ratio	0.76 (0.24–1.19)	2.0 (1.5–2.8)***

*$p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$

Table 4: Laboratory data of <60-month-old severely malnourished children categorised by their HIV status and malnutrition type.

	HIV-positive children		HIV-negative children	
	Oedema n = 53 median (IQR)	No oedema n = 70 median (IQR)	Oedema n = 119 median (IQR)	No oedema n = 73 median (IQR)
Haemoglobin (g/dL)	8.2 (6.4–9.6)	7.3 (6–9.1)	8.0 (6.1–9.3)	8.4 (6.7–9.8)
White blood cells (10^9/L)	11.0 (8.3–17)	7.2 (4.2–12)	10.0 (7.7–17)	11.0 (8.8–15)
Neutrophils (10^9/L)	6.2 (3.1–8.5)*	2.9 (2.3–7.7)	5.4 (3.5–8.8)	6.1 (3.2–9.0)
Neutrophils (%)	59.0 (34–70)	61.0 (37–73)	55.0 (48–66)	53.0 (38–63)
Monocytes (10^9/L)	667.0 (182–1246)*	153.0 (83–263)	217.0 (107–540)	412.0 (176–534)
Monocytes (%)	5.7 (2–10)*	2.0 (1.0–2.8)	2.0 (1–5)	3.5 (2–6.5)
Total lymphocytes (10^9/L)	3.3 (2.4–6.3)	2.5 (1.7–4.1)*	4.5 (2.6–7.2)	4.4 (3.6–5.7)
Lymphocytes (%)	39.0 (23–57)	36.0 (26–50)	39.0 (31–49)	42.0 (32–55)
$CD4^+$ cell counts	630.0 (305–1759)***	379.0 (123–713)	1354 (894–1914)***	1169 (682–1600)
$CD4^+$ cells (%)	20.0 (14–42)***	14.0 (5–25)	35.0 (29–44)***	27.0 (22–37)
$CD8^+$ cell counts	1046 (521–1896)	811.0 (462–1363)	822.0 (492–1367)**	595 (328–1054)
$CD8^+$ cells (%)	23.0 (20–39)*	41.0 (27–56)	15.0 (12–21)	16.0 (13–21)
$CD4^+/CD8^+$ cell ratio	0.9 (0.4–1.6)***	0.4 (0.1–0.9)	2.2 (1.6–3.0)	1.9 (1.2–2.8)

*p value < 0.05, **p value < 0.005, and ***p value < 0.001, comparing each HIV status group with the type of severe malnutrition.

non-oedematous malnutrition than in those with oedema. This difference persisted even after controlling for their HIV status (Figure 2).

Discussion

In this study, we have reviewed an old problem – severe malnutrition in children – by using modern techniques for assessing the immunocompetence that has developed over the last decades in response to the HIV/AIDS pandemic. We have used the up-to-date laboratory techniques for the assessment of lymphocyte subsets in recognised laboratories. Since some of the severely malnourished children are also HIV positive, it is now possible to describe the clinical and laboratory features of the two groups of patients: severely malnourished children with HIV infection and those without HIV infection. We have noticed the well-known fact that the clinical features of severe malnutrition and HIV/AIDS overlap in young children. This affects the possibility of an accurate clinical diagnosis of HIV infection in settings with poor resources and often with inadequate HIV-testing facilities, particularly in cases wherein the two conditions, namely, malnutrition and HIV infection co-exist [16]. Therefore, a question that arises is whether there are any clinical differences that may raise a suspicion of HIV infection in cases of severe malnutrition?

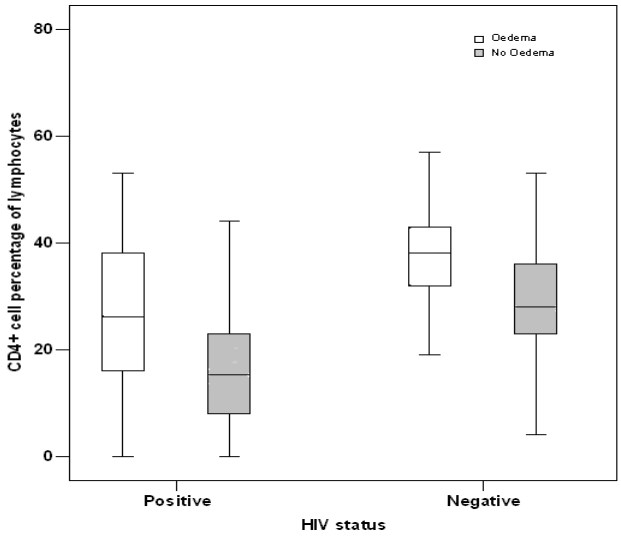

Figure 2
Box and whisker plot showing the median and the interquartile range of the percentages of $CD4^+$ cells in severely malnourished children who were grouped based on their HIV status and type of malnutrition.

In our study in Uganda, both the groups showed a high prevalence of multiple infections, including pneumonia, diarrhoea, bacteraemia, malaria, urinary tract infection and oral thrush. For respiratory, blood stream or urinary tract infections, no significant difference was observed with regard to the HIV status. The only two conditions that were over-represented among the HIV-positive children were persistent diarrhoea and oral thrush. In view of the remarkable difficulties encountered while clinically differentiating between malnutrition and HIV infection, we strongly support the establishment of routine counselling and testing for HIV-1 infection among paediatric patients with severe malnutrition in settings where HIV infection is an existing problem. In our study, we observed that there was a high acceptability of counselling and testing for HIV-1 infection; another reason for the absence of hesitation in organising routine counselling and testing for HIV-1 infection is that the study subjects were in the paediatric age group.

Table 5: Distribution of all severely malnourished children by malnutrition type, cellular immunological category and HIV status.

	HIV-positive children n (%)	HIV-uninfected children n (%)	Total
Oedema	**n = 53**	**n = 119**	**n = 172**
$CD4^+ \geq 25\%$*	28 (53)	119 (100)	171 (99)
$CD4^+$ 15%–24%**	15 (28)	0 (0)	0 (0)
$CD4^+ < 15\%$***	10 (19)	0 (0)	1 (1)
No oedema	**n = 70**	**n = 73**	**n = 143**
$CD4^+ \geq 25\%$*	15 (21)	50 (69)	65 (45)
$CD4^+$ 15%–24%**	22 (31)	15 (20)	37 (26)
$CD4^+ < 15\%$***	33 (62)	8 (11)	41 (29)

*No evidence of suppression, **Evidence of moderate suppression, ***Severe suppression

The drop-out cases in this study were mostly due to random factors, and we believe that these did not affect the selection of the study subjects in any systematic manner. In addition, the basic characteristics of the 315 of the 450 severely malnourished children analysed in this study were the same as those of the drop-out cases.

The median $CD4^+$ cell counts and percentages observed in this study were compared to the recently reported median $CD4^+$ counts and percentages of healthy Ugandan children younger than 5 years [18]. Among the HIV-uninfected children without oedema, as many as one-third had signs of immunosuppression with a $CD4^+$ percentage below 25%; this number was 1 in 12 in the HIV-uninfected children with oedema. Almost 80% of the HIV-positive children without oedema had signs of immunosuppression that was revealed as a $CD4^+$ cell percentage below 25%. Approximately half the HIV-positive children with oedema had $CD4^+$ counts below 25%. Very low $CD4^+$ cell percentages consistent with a laboratory diagnosis of AIDS have rarely been described in HIV-uninfected children with or without mixed infections. Reports on the proportions of T cell and $CD4^+$ cell percentages in severely malnourished children have shown inconsistent findings [3,4,19,20]. The difference in the results may be influenced by the differences in study designs and sample size.

Alterations in the haematological functions in malnutrition have been documented [17]. A recent study has reported cases of 5 malnourished children with mixed infection in whom the monocyte counts were higher than those in 4 malnourished children with only respiratory infection although their HIV status was not reported [3]. Therefore, both granulocyte and lymphocyte suppression observed in this study is an indication of reduced haemopoietic function, and the additional burden of HIV-1 infection appears to further reduce this function.

The $CD4^+$ cell percentages in this study were lower in children who presented with non-oedematous severe malnutrition, and this finding was consistent in both HIV-infected and uninfected groups. Earlier studies reported that oedematous malnutrition had lower T cell counts [19,21], while others found no difference in the T cell count with regard to the type of malnutrition [4]. The reason for these controversies is unclear. The only known fact is that severe malnutrition alters the immunological competence through a number of mechanisms, including apoptosis of the thymus gland [22, 23] and micronutrient deficiencies [24]. Likewise, the rapid destruction of the $CD4^+$ T lymphocytes by the HIV-1 virus has been well established. However, mechanisms leading to cellular immunological alterations in cases wherein severe malnutrition and HIV-1 virus infection co-exist are yet unclear.

It is interesting to notice that the HIV-positive children less often present with oedema, that is, oedema was present in just over 40% of the HIV-positive children, while it was seen in over 60% of the HIV-negative children. Severe wasting in the absence of oedema is a common feature observed in severe malnutrition with concurrent HIV infection [6,11,13-15]. The novel observation of this study was that the $CD4^+$ percentages were lower in both HIV-positive and HIV-negative children without oedema than in children with oedema. Both the above-mentioned observations appear to imply that the development of oedema requires a certain degree of immunocompetence, which is an interesting clue to the pathophysiology of oedema in severe malnutrition.

Conclusion

Severe protein energy malnutrition is associated with the depletion of the haematological and lymphocyte subsets, and this depletion is exacerbated by the presence of HIV-1 infection. Cell-mediated immunosuppression is more marked in non-oedematous severe malnutrition, regardless of the HIV status.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

All authors have participated in the design of the study, interpretation of the results, statistical analysis and writing of the manuscript. HB supervised patient recruitment, follow-up and data collection. All authors have read and approved the final manuscript.

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Paper IV

BMC Infectious Diseases

Research article

Bacteraemia among severely malnourished children infected and uninfected with the human immunodeficiency virus-1 in Kampala, Uganda

Hanifa Bachou*[1,2], Thorkild Tylleskär[2], Deogratias H Kaddu-Mulindwa[3] and James K Tumwine[1]

Address: [1]Department of Paediatrics and Child Health Makerere University Medical School P O Box 7072, Kampala Uganda, [2]Centre for International Health, University of Bergen, Norway and [3]Department of Microbiology Makerere University Medical School P O Box 7072, Kampala Uganda

Email: Hanifa Bachou* - hanifa.bachou@student.uib.no; Thorkild Tylleskär - thorkild.tylleskar@cih.uib.no; Deogratias H Kaddu-Mulindwa - dhkmulindwa@med.mak.ac.ug; James K Tumwine - jtumwine@imul.com

* Corresponding author

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Abstract

Background: To establish the magnitude of bacteraemia in severely malnourished children, and describe the types of bacteria and antimicrobial sensitivity by HIV status.

Method: Isolates were recovered from 76 blood specimens. Antibiotic susceptibility tests were performed using commercial antibiotic disks and demographic and clinical findings were recorded.

Results: Of the 450 children 63% were male; median age 17.0 months (inter quartile range, IQR 12–24) and 57% had oedema. 151 (36.7 %) of 411 tested HIV-positive; 76 (17.1%) of 445 blood specimens grew bacterial isolates; 58% were Gram negative – *S. typhimurium (27.6%)* and *S. enteriditis (11.8%)*. *Staph. aureus* (26.3%) and *Strep. pneumoniae* (13.2%) were the main Gram positive organisms. There was no difference in the risk of bacteraemia by HIV status, age < 24 months, male sex, or oedema, except for oral thrush (OR 2.3 CI 1.0–5.1) and hypoalbuminaemia (OR 3.5 CI 1.0–12.1). Isolates from severely immuno-suppressed children (CD4% <15%) were more likely to grow *Salmonella enteriditis* (OR 5.4; CI 1.6 – 17.4). The isolates were susceptible (≥ 80%) to ciprofloxacin, ceftriaxone and gentamicin; with low susceptibility to chlorampenicol, ampicillin (< 50%) and co-trimoxazole (<25%). Suspicion of bacteraemia had 95.9% sensitivity and 99.2% specificity. Among bacteraemic children, mortality was higher (43.5% vs 20.5%) in the HIV-positive; OR 3.0 (95%CI 1.0, 8.6).

Conclusion: Bacteraemia affects 1 in every 6 severely malnourished children and carries high mortality especially among the HIV-positive. Given the high level of resistance to common antibiotics, there is need for clinical trials to determine the best combinations of antibiotics for management of bacteraemia in severely malnourished children.

Background

Despite recent efforts aimed at reducing child mortality in resource poor countries, 11 million children under the age of five years die each year, mainly from infections and malnutrition [1]. Bacterial infections occur frequently in malnourished children and carry high case fatality. In Uganda, there is only one documented study of blood stream bacterial infection among severely malnourished children [2], and that study was carried out during the pre-HIV/AIDS era. Whether the HIV/AIDS pandemic has changed the pattern of bacterial infection and antimicrobial sensitivity is unknown. In Mulago, Uganda's national referral hospital, severe malnutrition has the highest case fatality compared to other paediatric illnesses, but the role of bacteraemia in this is not clear. The objective of the current study was to establish the magnitude of bacteraemia in severely malnourished children, and to describe the types of bacteria and antimicrobial sensitivity by HIV status.

Methods

We enrolled 450 children with severe malnutrition defined as symmetrical oedema involving at least the feet or severe wasting (weight for height less than 3 SD) or both. The children were aged below 60 months and admitted to the paediatric wards of Mulago, Uganda's national referral and teaching hospital. Two hundred and twenty were enrolled in September – November 2003 and 230 children in September – December 2004. The caregivers of these children gave informed consent. Anthropometric measurements were taken according to the WHO standard techniques and compared with National Centre for Health Statistics (NCHS) reference population [3] Severe malnutrition was defined as weight-for-height (or length for children less than 2 years) of < -3 z-score and/or presence of oedema. Children with a length below 49 cm were excluded from the study as the NCHS reference does not provide reference values for these children. A medical officer collected the children's demographic and health characteristics using a clinical history, physical examination and laboratory examinations of blood and urine specimens and chest x-ray at admission.

Blood culture and sensitivity

Blood specimens were obtained from 445 of the 450 children. Two millilitres of blood were drawn from a peripheral vein under aseptic condition after cleaning the skin with 70% alcohol and 2% tincture of iodine.

Each blood sample was inoculated into 2 culture bottles each containing 20 ml of Brain Heart Infusion Broth and incubated at 37°C for 24 hours after which bottles were observed for turbidity. From bottles showing turbidity, Gram's stain was done and inoculation made on to 7% sheep blood, chocolate and MacConkey agar, respectively. The plates were then incubated at 37°C for 18 – 24 hours. Blood and chocolate agar plates were incubated under carbon dioxide. Culture bottles that did not show turbidity were further incubated for up to 10 days. A total of 21/445 (4.7%) of the blood specimens grew contaminants.

Identification of culture isolates were done according to standard methods, for Gram negatives, AP120E was used followed by serological identification of salmonella species and coagulate test for *Staphylococcus aureus*, Optochin for *Streptococcus pneumoniae* and X and V factors for *Haemophilus influenzae*. The Kirby-Bauer diffusion method was used to test the susceptibility to the isolates on Muller-Hinton Agar-2 [4]. Commonly prescribed antibiotics were tested and graded as sensitive or resistant (Fa. Biomeriuex, France). Resistance was defined by the zone diameter below that given in standard operating procedure (NCCLS 2003). For example, all enterobacteriaceae are resistant to ampicillin when the zone diameter is less than 13 mm and considered sensitive when the zone diameter is greater than 17 mm.

HIV serology tests

Blood was taken in 5 ml EDTA vacutainer tubes (Becton Dickinson, Franklin lakes, NJ USA) every morning between 8–11 am by venipuncture and transported within 4 hours to the Uganda Virus Research Institute (UVRI) laboratory, Entebbe for serological testing. HIV testing was performed using a standard HIV algorithm of two enzyme-linked immunoassays (EIA) in parallel. Western blot, real time polymerase chain reaction (RT-PCR) was performed to confirm a positive EIA test for children below 18 months old and children with indeterminate results on EIA. Complete blood counts, including differential counts, were done using a Beckman Coulter counter.

Ethical considerations

Informed consent for participation in the study, including HIV testing, was obtained from the care givers who received pre-test and post-test counselling from an experienced multilingual study counsellor. The study was approved by the Regional Committee for Medical Ethics, Bergen, Norway (REK Vest), Makerere University Faculty of Medicine Ethics and Research Committee, Mulago Hospital Ethics Committee and the Uganda National Council for Science and Technology.

Statistics

The sample size was calculated using the formula by Kish [4]. Assuming a prevalence of bacteraemia among severely malnourished children to be 50%, also reported elsewhere [5] and a margin of error of 5% and 95% confidence, the minimum sample size for establishing the prevalence of bacteraemia was 380.

The statistical analysis was done using SPSS version 13 (SPSS Inc, Chicago, IL 60606, USA). For continuous variables medians were used to measure central tendency and inter quartile range (IQR) for the spread of the dependent variables. For categorical variables, proportions were compared using the chi-squared or Fisher's exact test where appropriate. The children were grouped by their gender (male, female), age groups in months (≤24 months and > 24 months; ≤12 months and > 12 months), presence of oedema, HIV test result (positive or negative) and blood culture result (bacteraemia or no bacteraemia). Logistic regression analysis was used to identify factors independently associated with bacteraemia.

Kaplan-Meier life tables and curves were used to determine survival functions and display data. Cox's proportional hazards model was used to compare survival with and without bacteraemia adjusted for age-group, sex, type of severe malnutrition and independent variables that had p values below 0.2 in the univariate analysis. Children were censored on the day of death. A 2-tailed p-value of < 0.05 was considered significant.

Results

Of the 450 severely malnourished children studied, 62.4% were males and the median age was 17.0 months (IQR 12–24, ranges 4 – 60). More than half (56%) of the children presented with oedema, and there was no difference by sex; OR 1.02 (95% CI 0.7–1.5). Commonly diagnosed infections on admission included respiratory tract infections (positive x-ray findings) and diarrhoea. Seventy six (17.1%) of the 445 blood specimens cultured, grew bacterial isolates.

Although 36.7% of the children tested positive for HIV-1, there was no significant difference in the proportion of children who had bacteraemia by HIV status, age-group, sex or presence of oedema (Table 1). However, the proportion of children with oral thrush who had bacterial infection was twice that of the children without oral thrush. Only oral thrush and hypoalbuminaemia remained significant after adjusting for other factors in a multiple regression analysis.

Of the 76 blood specimens growing bacterial isolates, 44 (58%) had Gram negative organisms, predominantly *Salmonella species* and *E. coli* (table 2). Among the Gram positive organisms, *Staphylococcus aureus* and *Streptococcus pneumoniae* predominated, table 2. There was no significant difference in the types or subtypes of blood bacterial organisms by HIV status. However, blood specimens from severely immuno-suppressed children (CD4% <15%) were more likely to grow *Salmonella enteriditis* species than those from children with higher CD4% (OR 5.4, 95% CI 1.7–17), even after adjusting for HIV status (OR 9.0; 95% CI 1.7–48). Of the 12/55 (28%) HIV negative children with CD4% of <15%, nine (75%) were aged between 9–23 months.

Blood specimens from children with oral thrush were more likely to grow *Salmonella typhimurium* (14.3%, 5/35) than those from children with with no oral thrush (4.6%, 13/280); (OR, 3.4, CI 1.14 – 10).

Isolates susceptibility to antibiotics

The bacterial isolates were mainly susceptible (≥ 80%) to ciprofloxacin, ceftriaxone, gentamicin and erythromycin.

Table 1: Characteristics, clinical and laboratory diagnosis and outcome of severely malnourished children below 60 months of age by presence or absence of blood stream infections, Mulago hospital, Uganda.

	Blood bacterial pathogens		Odds Ratio (95% Confidence interval)	
Characteristics	Present n/total (%)	Absent n/total (%)	Unadjusted	Adjusted
Age ≤ 24 months	59/353 (16.7)	17/92 (18.5)	0.89 (0.49–1.61)	0.78 (0.40–1.54)
Sex: male	48/279 (17.2)	28/166 (16.9)	1.02 (0.61–1.71)	0.99 (0.54–1.80)
Oedema	47/251 (18.7)	29/194 (14.9)	1.31 (0.79–2.18)	1.55 (0.81–2.96)
Hypothermia	3/24 (12.5)	21/327 (18.6)	0.62 (0.18–2.15)	
Oral thrush	15/54 (27.8)	61/391 (15.6)	2.08 (1.08–4.01)*	2.31 (1.04–5.11)*
Acute diarrhoea†	16/91 (17.6)	75/354 (21.2)	1.05 (0.57–1.92)	
Persistent diarrhoea††	15/81 (18.5)	66/364 (18.1)	1.13 (0.61–2.11)	
Respiratory infections	47/277 (17.0)	15/93 (16.1)	1.06 (0.56–2.01)	
Bacteruria	13/79 (16.5)	47/207 (22.7)	0.96 (0.49–1.89)	
Severe anaemia	2/56 (9.1)	20/253 (07.9)	2.3 (0.53–10.2)	
Malaria	5/36 (13.9)	71/406 (17.5)	0.76 (0.29–2.03)	
Hypokalaemia	38/178 (21.4)	38/262 (14.5)	1.60 (0.78–2.17)	1.44 (0.79–2.61)
Hypoalbuminaemia	71/367 (19.3)	5/73 (6.9)	3.26 (1.27–8.39)*	3.54 (1.04–12.1)*
Positive HIV status	30/149 (20.1)	39/259 (15.1)	0.42 (0.84–2.41)	1.67 (0.88–3.15)
CD4<15%	15/58 (13.8)	58/274 (21.2)	0.61 (0.27–1.36)	1.99 (0.76–5.22)

* p-value < 0.05, † frequent loose watery stools lasting ≤ 14 days, †† frequent loose watery stools lasting >14 days

Table 2: Number and percentages of bacterial pathogens isolated from blood specimens of severely malnourished children below 60 months of age at admission to, Mulago Hospital by HIV status

Bacteria pathogens	HIV+ n/total (%)	HIV -ve n/total (%)	Odds ratio (95% CI)
Gram positive (Total = 27)	14 (52)	13 (48)	1.31 (0.49 – 3.48)
Staphylococcus			
Aureus (n = 13)	8 (62)	5 (38)	
Coagulase negative (n = 5)	3 (60)	2 (40)	
Streptococcus pneumoniae (n = 9)	5 (56)	4 (44)	
Gram negative (Total = 41)	17 (42)	24 (58)	0.76 (0.29 – 2.03)
Salmonella			
Enteriditis (n = 9)	3 (33)	6 (67)	
Typhimurium (n = 19)	8 (42)	11 (58)	
Typhi(n = 5)	2 (40)	3 (60)	
Escherichia coli(n = 6)	3 (50)	3 (50)	
Haemophilus. Influenzae (n = 2)	1(50)	1 (50)	

They had low susceptibility to chlorampenicol, ampicillin (< 50%) and co-trimoxazole (< 25%), table 3. Susceptibility to ceftazidime, ampicillin and chloramphenicol was significantly higher for bacterial pathogens isolated from HIV positive compared to the HIV negative (table 4). Intermediate resistance to specific antibiotics was also observed (2 to ceftriaxone, 1 to ceftaxidime, 3 to cefuroxime, 2 to ampicillin and 1 to chloramphenicol).

Mortality

Although the mortality among the 76 children who had bacteraemia was higher (28.9% vs. 23.0%) than among the 369 without bacteraemia, the difference was not significant; OR 1.4 (95% CI 0.8–2.4), table 5.

Among the children with bacteraemia, mortality was higher (43.5% vs. 20.5%) in the HIV positive than the HIV negative; OR 3.0 (95% CI 1.01–8.6). This difference was still apparent when the survival of the children with bacteraemia was analyzed by the log rank test (p = 0.02). For the children without bacteraemia, the test of equality of survival distributions by HIV status was not significant (p = 0.07, figure 1).

Discussion

In this study we report the pattern of bacteraemia amongst severely malnourished children in Mulago hospital, Uganda, where the prevalence of HIV infection among paediatric patients is high [7]. The prevalence of bacteraemia of 17% among the severely malnourished children in the current study is about the same as the 13% reported by Philipps and Wharton [2] in the same hospital in the pre-HIV/AIDS era, and comparable to the 18.7% recently reported from Nairobi by Nooran et al [8]. Nonetheless, a positive HIV test did not significantly increase the prevalence of bacteraemia. This is in keeping with several stud-

Table 3: Number and percentages of susceptibility of bacterial pathogen isolated from blood specimens of severely malnourished children below 60 months of age to selected antibiotics by HIV status.

	Staphylococcus		Streptococcus Pneumoniae	Salmonella			Escherichia Coli	Haemophilus
Antimicrobials	Aureus n/total (%)	CoN† n/total (%)	n/total (%)	Typhi n/total (%)	Enteriditis n/total (%)	T. murium‡ n/total (%)	n/total (%)	Influenza n/total (%)
Co-trimoxazole	4/17 (23)	0/3 (0)	0/11 (0)	1/5 (20)	2/9 (22)	6/21 (29)	0/6 (0)	0/2 (0)
Ampicillin	13/20 (65)	2/5 (40)	7/12 (58)	1/5 (20)	2/9 (22)	0/21 (0)	1/6 (17)	0/2 (0)
Augmentin*	12/14 (86)	2/3 (67)	10/11 (91)	3/5 (60)	2/8 (25)	4/21 (19)	1/6 (17)	1/2 (50)
Chloramphenicol	12/19 (63)	3/5 (60)	8/11 (73)	0/5 (0)	3/9 (33)	6/21 (29)	3/6 (50)	1/2 (50)
Cloxacillin	3/5 (60)	0/1 (0)	5/8 (62)	-	-	-	-	-
Cefuroxime	7/14 (50)	0/4 (0)	4/10 (40)	2/5 (40)	8/9 (89)	12/21 (57)	4/5 (80)	0/2 (0)
Ceftaxidime	9/15 (60)	1/3 (33)	5/6 (83)	1/5 (20)	0/2 (0)	4/7 (57)	1/4 (25)	1/1 (100)
Erythromycin	8/13 (61)	2/3 (67)	6/6 (100)	-	-	-	-	1/1 (100)
Gentamicin	15/17 (88)	4/5 (80)	3/7 (43)	4/5 (80)	9/9 (100)	16/21 (76)	5/6 (83)	1/2 (50)
Ceftriaxone	13/19 (68)	4/4 (100)	8/11 (73)	4/5 (80)	9/9 (100)	19/21 (91)	5/5 (100)	2/2 (100)
Ciprofloxacin	9/10 (90)	4/5 (80)	3/4 (75)	5/5 (100)	2/2 (100)	7/7 (100)	3/3 (100)	1/1 (100)

* Amoxicillin-clav, †Coagulase Negative, ‡Typhimurium

Table 4: Number and percentages of susceptibility of bacterial pathogen isolated from blood specimens of severely malnourished children below 60 months of age to selected antibiotics by HIV status.

Antibiotics	HIV status		Odds ratio (95% CI)
	positive n/total (%)	negative n/total(%)	
Co-trimoxazole	5/24 (21)	9/39 (23)	0.90 (0.25 – 3.24)
Ampicillin	16/30 (53)	12/39 (31)	0.33 (0.12 – 0.93)
Augmentin	14/25 (56)	19/37 (51)	1.04 (0.38 – 2.87)
Chloramphenicol	16/29 (55)	14/39 (36)	0.35 (0.13 – 0.95)
Cloxacillin	2/4 (50)	4/7 (57)	1.33 (0.11 – 16.0)
Cefuroxime	16/21 (76)	24/37 (65)	0.88 (0.31 – 2.45)
Ceftazidime	13/18 (72)	8/17 (47)	0.21 (0.05 – 0.9)
Erythromycin	8/12 (67)	8/8 (100)	2.67 (0.24 – 30.1)
Gentamicin	21/27 (78)	29/36 (81)	1.09 (0.32 – 3.71)
Ceftriaxone	27/32 (84)	35/39 (90)	0.16 (0.02 – 1.42)
Ciprofloxacin	14/15 (93)	14/15 (93)	1.0 (0.06 – 17.6)

ies of bacteraemia in the HIV/AIDS era [8,9], but different from Berkeley's [10] study in which HIV and malnutrition were independent risk factors for bacteraemia. This difference might be due to the fact that the current study was carried out on only severely malnourished children with a high risk of dying.

Gram negative organisms, especially non typhoidal *salmonella species*, were the predominant cause of bacteraemia in severely malnourished children, supporting early results from Uganda [2] and recent studies from Kenya, Malawi and Ethiopia [8,11-13].

Although there was no difference in the types of bacterial organisms by HIV status, blood specimens from severely immuno-suppressed children were more likely to grow *Salmonella enteriditis*. The mechanism for this is not very clear and may include the difficulty in clearing salmonella infections from infected macrophages and weak immune system, HIV may predispose the host to infection with *Salmonella enteriditis* [14] and this, in turn, promotes the production of HIV in the macrophages of the gastrointestinal tract mucosal cells, thus completing a vicious cycle. Although some of the non typhoidal salmonella in the current study were unusual, they were all from the blood cultures and from patients residing in the slums of Kampala city.

We also found a high proportion of Gram positive organisms particularly *Staphylococcus aureus*. The reason for the predominance of *Staphylococcus aureus* in this series is not clear as there was no associated skin ulceration. It is possible that vitamin A deficiency in severely malnourished patients [15] might have contributed to this. Several studies have suggested that vitamin A deficiency predisposes to *Staphylococcus aureus* through phagocyte dysfunction and decreased complement activity [16]. In Uganda, the national health program includes Vitamin A supplementation twice a year for all the children below 5 years of age, from the age of 9 months. Vitamin A is also routinely

Table 5: Number and percentages of outcome of severely malnourished children who had bacterial blood stream infections at admission to Mulago hospital, Uganda

Organism	Outcome status				
	Dead		Alive		
	n	(%)	n	(%)	OR (95% CI)
Staphylococcus aureus	3	(20)	12	(80)	1.8 (2.8 – 6.7)
Coagulase negative	1	(20)	4	(80)	1.7 (0.2 – 16)
Streptococcus pneumoniae	4	(40)	6	(60)	1.8 (0.5 – 07)
Haemophilus influenza	1	(50)	1	(50)	-
Salmonella enteriditis	1	(11)	8	(92)	3.6 (0.4 – 31)
Salmonella typhi	0	(0)	5	(100)	-
Salmonella typhimurium	6	(29)	15	(71)	1.0 (0.3 – 3.1)
Escherichia coli	6	(100)	0	(0)	4.4 (2.8 – 6.7)

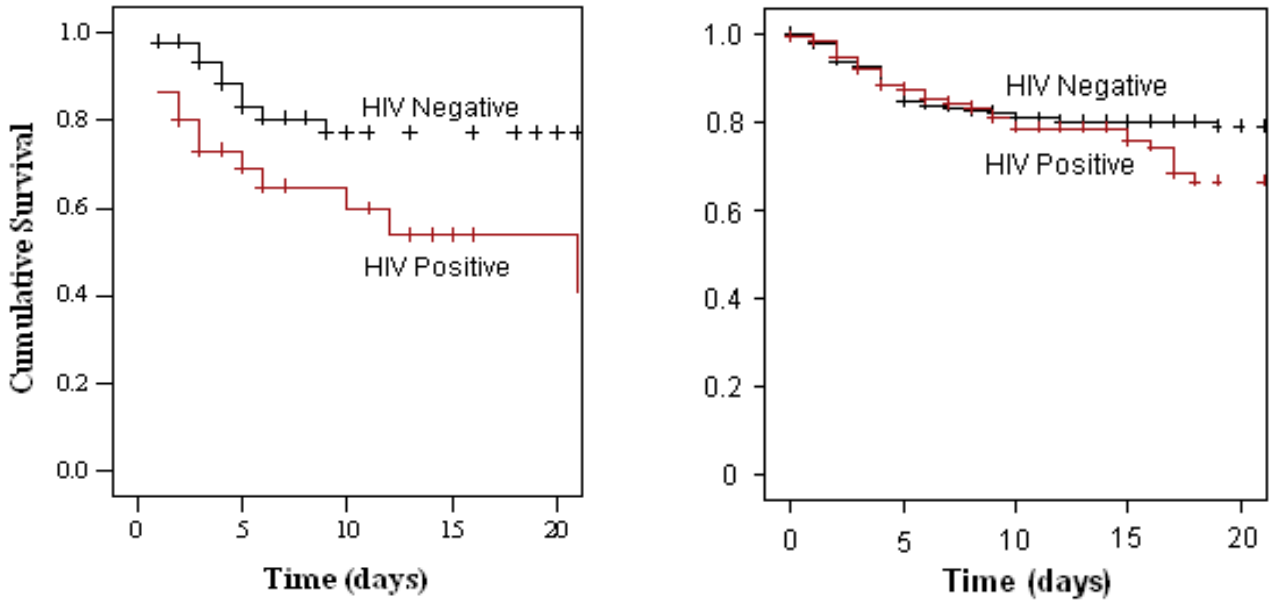

Figure 1
Kaplan-Meier survival curves of HIV positive and HIV negative children by blood culture positive and negative result.

given as treatment to all children suffering from measles, tuberculosis, severe malnutrition and severe pneumonia. Other possible risk factors that could have contributed to *Staphylococcus aureus* include concurrent viral infections, chronic lung diseases in HIV positive children and prior hospitalization. However, none of the children had been hospitalized two weeks prior to the study.

We found a very low proportion of *H. influenzae* infection in these children and this may be explained by the incorporation of HiB vaccine into the expanded programme on immunization (EPI) in Uganda from 2002.

Our study demonstrated high bacterial resistance to commonly used antibiotics such as co-trimoxazole, ampicillin and chloramphenicol among both HIV positive and HIV negative children. These findings raise great concern as ampicillin, in combination with gentamicin, is routinely given to all children admitted with severe malnutrition at Mulago hospital [17] However there was high susceptibility to ciprofloxacin, ceftriaxone and gentamicin regardless of HIV test status and this concurs with recent finding from Kenya [8].

Surprisingly, blood isolates from HIV infected children were more susceptible to ampicillin and chlorampenicol than those from HIV negative children. This finding is at odds with results from an Ethiopian study which reported that isolates recovered from HIV-positive patients were significantly resistant to many of the antibiotics tested when compared to the isolates from HIV-negative patients [18]. However a recent study from Thailand, of antimicrobial susceptibility tests of bacterial pathogens from blood cultures of HIV-infected patients, found that Salmonella species were highly sensitive to amoxicillin/clavulanate, gentamicin, and ciprofloxacin [19]. The difference in sensitivity patterns of salmonellae species may probably be attributed to difference in accessibility and use of antibiotics.

These results leave us in an important dilemma. The organisms exhibited very low in vitro susceptibility to one of the drugs (ampicillin) currently recommended in combination with gentamicin for the management of presumed bacteraemia in severely malnourished children. However they showed high susceptibility to gentamicin and ciprofloxacin. This calls for further studies to determine the most feasible combination of antibiotics for the management of bacteraemia in severely malnourished children in this setting. In conformity with other studies, our study did not find clinical signs or symptoms that could be reliably used to predict bacteraemia [9,20].

The mortality among severely malnourished children with bacteraemia of 28.9% was comparable to findings from other centres in sub-Saharan Africa [8,11,13]. Overall, there was no significant association between bacteraemia and mortality in this vulnerable group of children.

However among the children with bacteraemia, mortality was much higher in the HIV-positive than among the HIV-negative, table 5. This underscores the importance of early diagnosis and use of efficacious antibiotics [21]. In the current study we did not observe any significant relationship between outcome and age of the children, which is consistent with results of a recent study from Kenya [22].

A limitation of this study is the lack of information on prior use of antimicrobials and previous history of hospitalization that may be associated with bacterial resistance and types of isolates. However, the information on underlying diseases was collected using the clinical history, physical examination laboratory tests and chest x-ray. We used isolates from two samples of children form two different years. However, the severely malnourished children from the two samples came from the same community served by the hospital and the same methodology was used at the same seasonal periods, the same hospital setting and the same laboratories. The study was conducted in only one hospital in the country and may not be representative of the larger Ugandan population.

Further more, the selection of specific seasons may have a bearing on the spectrum of pathogens identified as well as on the severity of malnutrition. The study was carried out between September and December, which is the peak season for severe malnutrition in Uganda. Unfortunately, it was not possible to determine the effect of seasonality on non-typhoidal salmonellae.

Conclusion

Bacteraemia (both Gram negative and Gram positive organisms) affects one in every 6 severely malnourished children and carries high mortality especially among the HIV-positive children. Given the high level of resistance to commonly used antibiotics, there is need for clinical trials to determine the most feasible combination of antibiotics (cheapest most effective, given orally) for the management of bacteraemia in severely malnourished children in this setting.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

All authors participated in the design of the study, interpretation of the results, statistical analysis and writing the manuscript. HB supervised patient recruitment, follow-up and data collection. All authors read and approved the final manuscript.

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