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CRITICAL CARE IN LOW RESOURCE SETTINGS

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Critical Care in Low Resource Settings

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By

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To Ulrika, Alva and Frida

The best is the enemy of the good
Voltaire

ABSTRACT

Background: Critical care is the care of patients with immediately life-threatening disease or injury. The substantial global burden of critical illness is especially high in low resource settings. There is a striking lack of knowledge about the quality of critical care in such settings and about how to improve care.

Aim: To assess the quality of critical care in low resource settings and to evaluate methods for identifying critical illness and improving critical care.

Methods: All studies were conducted in Tanzania, a low-income country in East Africa. Quality standards for critical care in low resource settings were developed and used to evaluate a sample of ten hospitals in a cross-sectional survey. Deranged vital signs were studied in patients at admission to hospital and to the Intensive Care Unit (ICU). Severe derangements were defined as "danger signs" and combined to form compound scores. The relationships between in-hospital mortality and deranged vital signs were assessed using prospective cohort studies. A context-appropriate vital signs directed therapy (VSDT) protocol was designed and implemented on an ICU using a multi-faceted approach. The effects of VSDT on the acute treatment of critically ill patients and on mortality rates were evaluated.

Results: There were deficits in infrastructure, routines and training for critical care. In contrast, a majority of the necessary equipment and drugs were available. Single danger signs, both at admission to hospital and to ICU were associated with mortality and were as useful as the more complex compound scoring systems. Danger signs were common among patients on ICU and the identification of a danger sign was rarely followed by an acute treatment. The in-hospital mortality rate for patients cared for on ICU was 50%. The VSDT protocol led to improvements in the care given for deranged vital signs. The mortality rate for patients admitted with hypotension was reduced following the implementation of VSDT, but not for all patients.

Conclusions: There is a lack of good quality critical care in low resource settings. Single deranged vital signs identify critical illness and introducing a vital signs directed therapy protocol can improve the acute treatment of critically ill patients and reduce mortality rates for some patients.

Keywords: Critical Care; Vital Signs; Developing Countries; Emergency Treatment; Hospital Mortality; Global Health; Quality of Health Care

LIST OF SCIENTIFIC PAPERS

I. **Use of an early warning score and ability to walk predicts mortality in medical patients admitted to hospitals in Tanzania**
Rylance J, Baker T, Mushi E, Mashaga D.
Trans R Soc Trop Med Hyg 2009; 103: 790-794

II. **Emergency and critical care services in Tanzania: a survey of ten hospitals**
Baker T, Lugazia E, Eriksen J, Mwafongo V, Irestedt L, Konrad D.
BMC Health Services Research 2013;13:140

III. **Single deranged physiologic parameters are associated with mortality in a low-income country**
Baker T, Blixt J, Lugazia E, Schell CO, Mulungu M, Milton A, Castegren M, Eriksen J, Konrad D.
Critical Care Medicine 2015;43(10):2171-2179

IV. **Vital Signs Directed Therapy: Improving care on an Intensive Care Unit in a low-income country**
Baker T, Schell CO, Lugazia E, Blixt J, Mulungu M, Castegren M, Eriksen J, Konrad D.
Submitted manuscript

CONTENTS

LIST OF ABBREVIATIONS

ABC	Airway Breathing Circulation
APACHE	Acute Physiology and Chronic Health Evaluation
AUROC	Area Under the Receiver Operating Characteristic Curve
BP	Blood Pressure
CI	Confidence Interval
ETAT	Emergency Triage And Treatment
EWS	Early Warning Score
GCS	Glasgow Coma Scale
GDP	Gross National Product
GDT	Goal Directed Therapy
GNI	Gross National Income
HIV/AIDS	Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome
ICU	Intensive Care Unit
LIC	Low Income Country
MKAIC	Muhimbili-Karolinska Anaesthesia & Intensive Care Collaboration
NEWS	National Early Warning Score
NGO	Non-Governmental Organisation
OR	Odds Ratio
PR	Prevalence Ratio
ROC	Receiver Operating Characteristic
RRT	Rapid Response Team
SAPS	Simplified Acute Physiology Score
UK	United Kingdom
USA	United States of America
VSDT	Vital Signs Directed Therapy
WHO	World Health Organisation

INTRODUCTION

Scholastica, a 20 year old woman, is taken by her family to a district hospital in Tanzania. She is breathless and unable to talk or walk. She has pneumonia. She is about to die. The staff on duty recognise that she is critically ill and admit her to the Intensive Care Unit, calling a doctor for urgent help. Over the next three days, they keep her airway open, give her oxygen to help her breathe, fluids to treat her shock and antibiotics to cure her infection. She improves. She survives. She has been given *Critical Care*.

The idea for studying critical care in low resource settings came from my experiences in Tanzania in 2005-6. My wife, Ulrika, and I were working as volunteer doctors in St Joseph's Hospital, Peramiho. I was struck by the huge number of patients like Scholastica who arrived at the hospital in a critical state and needed immediate care. Together with the dedicated doctors and nurses at Peramiho we worked to build up a system for giving critical care that could function effectively despite the shortage of resources.

Two years later I was part of the group that started the Muhimbili-Karolinska Anaesthesia and Intensive Care Collaboration, a partnership between the two university hospitals in Tanzania and Sweden. The collaboration has since grown into the Life Support Foundation, aiming to improve the access to, and quality of, critical care and basic life-saving interventions. Much of the work in this thesis has been done within these organisations.

I am convinced that good quality critical care could save many lives throughout the world. My hope is that the work in this thesis from low resource settings in Tanzania will add knowledge and contribute to global critical care. **Study I** investigates patients arriving at two centres in Tanzania, assessing the information that their vital signs provide about their risk of dying. **Study II** is a survey of the available structures and routines for emergency and critical care in ten hospitals in Tanzania. **Study III**, from an intensive care unit in a university hospital, assesses how sick the patients are, their outcomes, and the relationship between their vital signs and in-hospital mortality. **Study IV** moves from observational to interventional research, and evaluates the improvements to practice and mortality reductions following the introduction of a newly developed vital signs directed therapy protocol.

BACKGROUND

CRITICAL ILLNESS

In this thesis, critical illness is defined as *any immediately life-threatening disease or injury*. It is the most severe stage of acute disease, and if left untreated, often leads to the death of the patient (Fig. 1).

Critical illness does not respect age, gender or social status. Nor is critical illness confined within one medical specialty. Newborn babies, children, adults, pregnant women, patients suffering from infectious diseases, non-communicable diseases or trauma – all can become critically ill.

There are no reliable epidemiological data about the global burden of critical illness, but critical syndromes such as sepsis and acute lung injury are common, suggesting a large, underappreciated burden of *several million deaths* annually (1). The global trends of ageing and urbanised populations, therapeutic advances that lead to the treatment of high risk patients, increasing availability of surgical services and the consequences of natural and man-made disasters will further increase this burden (1-3).

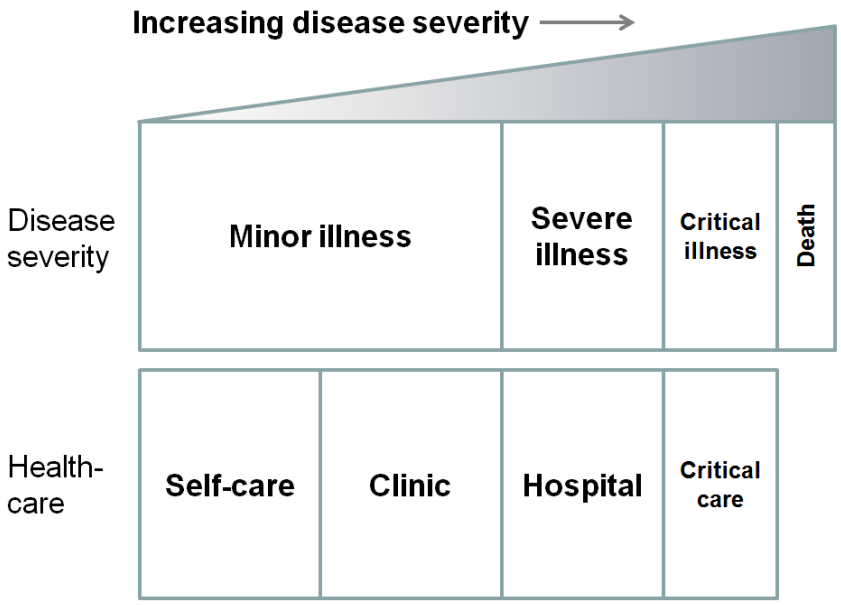


Fig. 1 Acute disease severity and appropriate healthcare

CRITICAL CARE

Critical care is the *care given to any patient with critical illness* (Fig. 1). It is sometimes falsely understood as synonymous with care given on intensive care units (ICUs). However, critical illness often occurs outside of ICUs, such as in emergency departments, on wards, in operating theatres and outside hospital (4). Critical care emphasises the life-saving and supportive therapies that maintain vital organ functions, rather than the definitive treatments and cures that are the focus of other medical specialties. The core of critical care is captured by the ABC mnemonic *Airway-Breathing-Circulation*, first used in the 1950s for

cardiopulmonary resuscitation (5). ABC is widely used by critical care practitioners throughout the world, reminding us of the priorities when assessing and treating the critically ill.

History of critical care

The introduction of the most basic principle of critical care, close observation, is often attributed to Florence Nightingale. In the Crimean War in the 1850s, she rearranged the hospital beds so the most seriously ill were near to the nursing station. In the first decades of the 20th century, critical care developed with recovery units for post-operative patients, and in the Second World War, shock units provided resuscitation for severely injured soldiers. In Borås in Sweden in 1952, a post-operative unit opened that could provide advanced monitoring and care (6). The first ICU opened in Copenhagen in the 1950s when ventilation support was used to treat patients with polio and respiratory failure, saving hundreds of lives (7-9).

Critical care in high resource settings

Since the 1950s, ICUs have been transformed. A typical ICU in the 21st century is a technologically-advanced, specialised medical unit managing patients with multi-organ failure (Fig. 2). Critical care in such units can be found in high resource settings throughout the world (10-12).

depositphotos.com

Fig. 2 Modern Intensive Care Unit

Despite the abundance of expensive equipment and therapies in modern ICUs, the principles of ABC remain fundamental. A critical care clinician's daily practice revolves around supporting the patients' airway, breathing and circulation. The central importance of basic care is seen in the increasing focus on patient safety, standardised approaches, guidelines and checklists (13-15).

The need for critical care is growing as the burden of critical illness increases. The proportion of hospital services dedicated to critical care is rising (Fig. 3) and critical care is moving outside its traditional home in the ICU (7). ICU outreach teams and "rapid response systems" have been established in hospitals to provide care to critically ill ward patients (16-18). These teams use the principles of critical care and ABC, often without high-tech intensive care facilities, to prevent deterioration and reduce mortality (18,19).

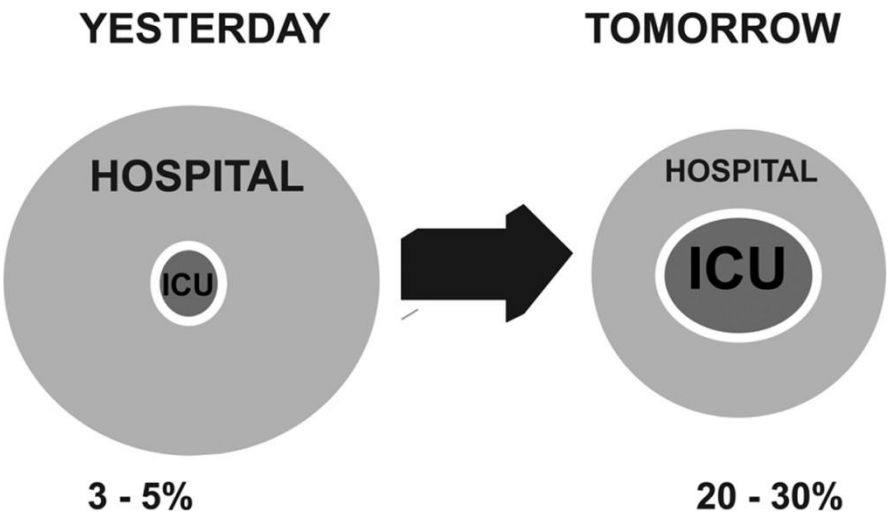


Fig. 3 Changing place of the ICU within the hospital
Schematic to demonstrate the increasingly large place that the ICU of tomorrow will occupy within the hospital system compared with the past, with ICU beds representing a much larger percentage of total hospital beds.

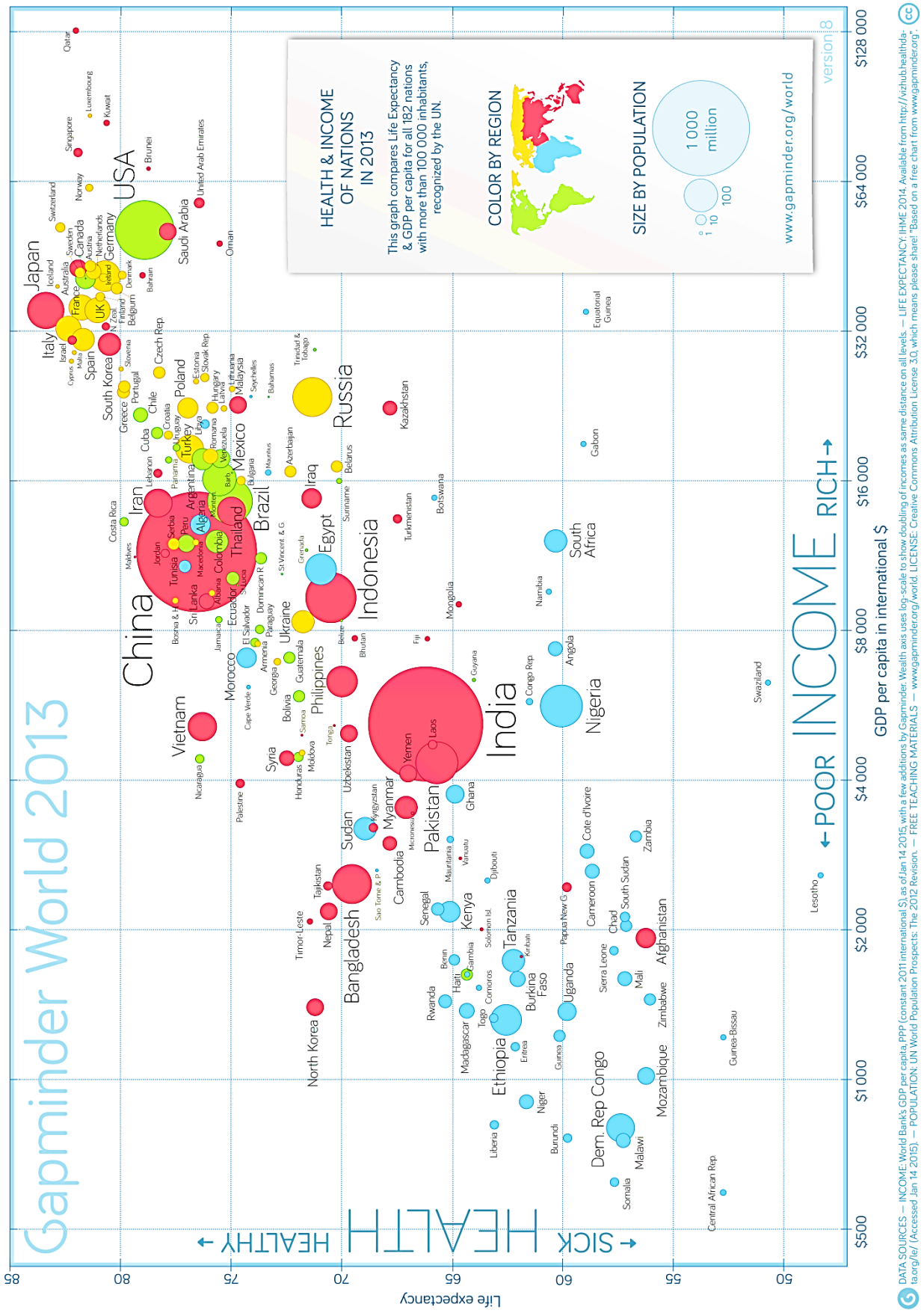
Reproduced with permission from Vincent, J.L. Critical Care 2013; 17: S2

LOW RESOURCE SETTINGS

Global resources are not equally distributed (Fig. 4). The term *low resource setting* is used in this thesis for settings with few material and financial means. In healthcare this can entail limited access to medication, equipment and supplies, under-developed infrastructure and a lack of trained personnel. In low resource settings, a large proportion of the population live under the poverty line of $1.25 per day, and face challenges concerning health information, access to healthcare, transportation and out-of-pocket payments.

Low resource settings are mostly found in countries defined by the World Bank as low-income countries (LICs) (20). Low-income countries spend on average $32 on health per person per year while high-income countries spend $4600 (21). Low-income countries have an average of 2.5 doctors per 10,000 population while high-income countries have 28.7 (21).

However, *low resource settings* and *low-income countries* are not always synonymous. There are also resource inequalities *within* countries. For example, in some countries the proportion of births attended by skilled health workers differs by up to 80% between the richest and poorest subgroups (22). Richer subgroups in low-income countries access high resource healthcare facilities that are often privately owned while poorer subgroups in middle-income countries utilise low resource, state-run facilities (23-25).



Based on a free chart from www.gapminder.org

Fig. 4 Health and income of nations

Critical illness in low resource settings

Low resource settings have a disproportionate amount of the global burden of critical illness. Over 90% of global trauma deaths, maternal deaths and deaths from pneumonia, meningitis and other infections are in low and middle income countries (26-28). Underlying poor health status, malnutrition, or HIV can cause patients to be weak. Presentation to hospital is often late due to long travel distances and an inability or reluctance to pay hospital fees – half of child deaths in hospital occur within 24 hours of arriving at hospital (29). A quarter of medical admissions were critically ill in one South African study (30). Acute disasters such as the recent Ebola outbreak in West Africa can cause a further increase in critical illness (31,32).

Critical care in low resource settings

All of these critically ill patients require critical care. Do they receive it? There is a striking lack of knowledge about critical care in low resource settings (33). Several reviews describe under-developed critical care (1,34-37). Uganda and Nepal, the only countries with published data, have only one and seventeen ICU beds per million inhabitants respectively (38,39) (cf. Sweden with 58 and Germany with 292) (40). Hospitals in Africa do not have the necessary critical care resources to follow international sepsis guidelines (13,41). The sparse data that have been published from ICUs in low resource settings report high mortality rates of 27-82% (42-46).

It is not fully understood why critical care would be so neglected in low resource settings. Possible explanations include a lack of capacity in training institutions; deficient physical structures; missing drugs and equipment; a health system focus on vertical, disease-based programmes; too few critical care physicians; an absence of clinical checklists or guidelines and high rates of staff burnout (33,35,47-51). Underlying this is a lack of prioritisation by policy makers. Critical care is usually absent from national and international health system policies and plans; there is chronic underfunding and a lack of understanding that critical care is possible in low resource settings (52).

VITAL SIGNS

A key element of critical care is the use of vital signs. Vital signs (heart rate, respiratory rate, blood pressure, conscious level, body temperature, oxygen saturation) are markers of illness severity. Deranged vital signs correlate with adverse outcomes such as admission to the ICU, unexpected cardiac arrest and death (53-60).

Although checking a patient's vital signs is a common hospital routine in both high and low resource settings, they are not always checked regularly (61) and there can be deficiencies in recognising when they are signalling clinical deterioration (62). Using vital signs for the identification and treatment of critical illness is recommended and can lead to improved

outcomes (61,63,64). The practise of triage – prioritising patients by clinical need – is frequently deployed in emergency departments and is usually based on vital signs (65,66).

In recent years, several initiatives in high-income countries have formalised the use of vital signs to improve the care of the critically ill. Early warning scores (EWS), such as the National Early Warning Score (NEWS) used throughout the United Kingdom, grade ward patients by aggregating vital sign derangements to provide a single measure of illness severity. With increasing score the risk of mortality rises (56,67,68). Rapid Response Teams (RRT) consisting of staff specialised in critical care can be called to assess patients on the wards when vital sign derangements go beyond a pre-defined trigger level (18). Goal Directed Therapy (GDT) uses specified treatments to bring a patient's vital signs towards normalised levels (69). GDT was seen to reduce mortality by 30% in patients with sepsis in the USA in 2001 (70) and led to a significant reduction in complications and hospital stay in patients undergoing major surgery in the UK (71).

EWS, RRT and GDT have become a mainstay of critical care in hospitals in many parts of the world including at Karolinska University Hospital in Sweden (19). Similar initiatives with appropriate triggers and interventions for low resource settings have not been greatly studied.

GLOBAL HEALTH

This thesis lies within the discipline of global health, "an area for study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide" (72). Most global health work has been on prevention at a population level with initiatives such as clean water, vaccinations and mosquito nets. However, a recent focus has been on health policies and systems – improving the way that societies organise themselves to achieve health (73). This includes considerations about the structure of care in health facilities, the organisation of clinical care, and the relative strengths of preventative and curative care.

Increasing access to care and the quality of clinical care is the central aim of the current global health drive towards Universal Health Coverage (74). Proponents of an increased emphasis on clinical care include those calling for a roll-out of surgical services to all parts of the world (2,75,76). Many people worldwide lack access to safe and affordable surgery, and several studies have found surgery and other hospital-based clinical care to be as cost-effective as preventative care (76-80).

Although global guidelines have been developed for clinical services such as trauma (81), paediatrics (82) and emergency obstetric care (83), critical care has been neglected by the global health community. Several authors have recognised the pressing need for research to investigate the current state of critical care services, to find appropriate ways of identifying patients with critical illness, and to develop and test methods for improving critical care when resources are limited. (35,52,84).

AIM OF THE THESIS

Overall aim

To assess the quality of critical care in low resource settings and to evaluate methods for identifying critical illness and improving critical care.

Specific aims

- To assess the quality of critical care in low resource settings
- To investigate the association between deranged vital signs and mortality in low resource settings and to evaluate whether single deranged vital signs are as useful as a compound scoring system
- To evaluate if a vital signs directed therapy (VSDT) protocol improves the acute treatment of patients with deranged vital signs
- To evaluate if VSDT improves outcomes for critically ill patients

MATERIALS AND METHODS

STUDY SETTING

Tanzania

All four studies have been conducted in the United Republic of Tanzania in East Africa. Since independence in the 1960s, Tanzania has been a stable democratic republic, without major armed conflicts. It is a low-income country with an annual Gross National Income (GNI) in 2014 of $930 per capita. GNI has grown at more than 5% per year since 2005 but 43% of the 49 million population live on less than $1.25 per day (85).

Fig. 5 Africa

Modified from depositphotos.com

In 2014 Tanzania was ranked 159 out of 186 countries in the United Nations Human Development Index (86).

	Tanzania	Sweden
Population	49 million	9.6 million
GNI per capita	$930	$61,600
Per capita annual expenditure on healthcare	$42	$5,293
Expenditure on healthcare as % of GDP	7.1%	9.6%
Number of doctors	1,470	37,000
Number of doctors per 10,000 population	0.3	39.3
Number of nurses	21,000	106,000
Life expectancy (years)	63	82
Maternal mortality (ratio per 100,000 live births)	410	4
Newborn mortality (per 1000 live births)	21	2
Child mortality (under 5s per 1000)	52	3
Female Adult mortality (deaths aged 15 - 60 per 1000)	24	4

Table 1 Health indicators in Tanzania and Sweden

GNI Gross National Income GDP Gross Domestic Product

Sources: World Bank (85) and World Health Organisation (21)

Health in Tanzania

As can be seen in Fig. 4, Tanzania is situated roughly in the centre of LICs in terms of health. Average life expectancy is 63 years, child mortality is 52/1000 and maternal mortality is 410 per 100,000 live births (Table 1). Recent years have seen an improvement in health statistics, with a halving in child and maternal mortality since 1990 (21).

The health system in Tanzania is organised as a pyramid. At the base are the village health workers and primary care clinics. Each of the 132 districts has a district hospital, and the 18 regional hospitals provide referral and more specialized care. At the tip of the pyramid are the four referral hospitals, including the largest, Muhimbili National Hospital in Dar es Salaam. Almost one-third of health services in Tanzania are run by non-governmental organisations (NGOs), in particular faith-based organisations (87).

There are several ongoing challenges for the health system in Tanzania. The rising trend of non-communicable diseases such as diabetes, heart disease and cancer at the same time as the long-standing infectious diseases has led to a double disease burden (88). There is a large shortage of health workers – the country has only 20% of the number required according to the Ministry of Health's guidelines (89,90). Clinical supervision and quality control of health facilities are problematic and national guidelines are not reliably implemented into practice (90-92). The vertical programs such as those for HIV/AIDS, malaria and TB risk competing for health workers and are not always integrated into overall health system strengthening (92). Providing good quality care in health facilities in the context of these challenges can be difficult (93-95).

STUDY AREAS AND POPULATION

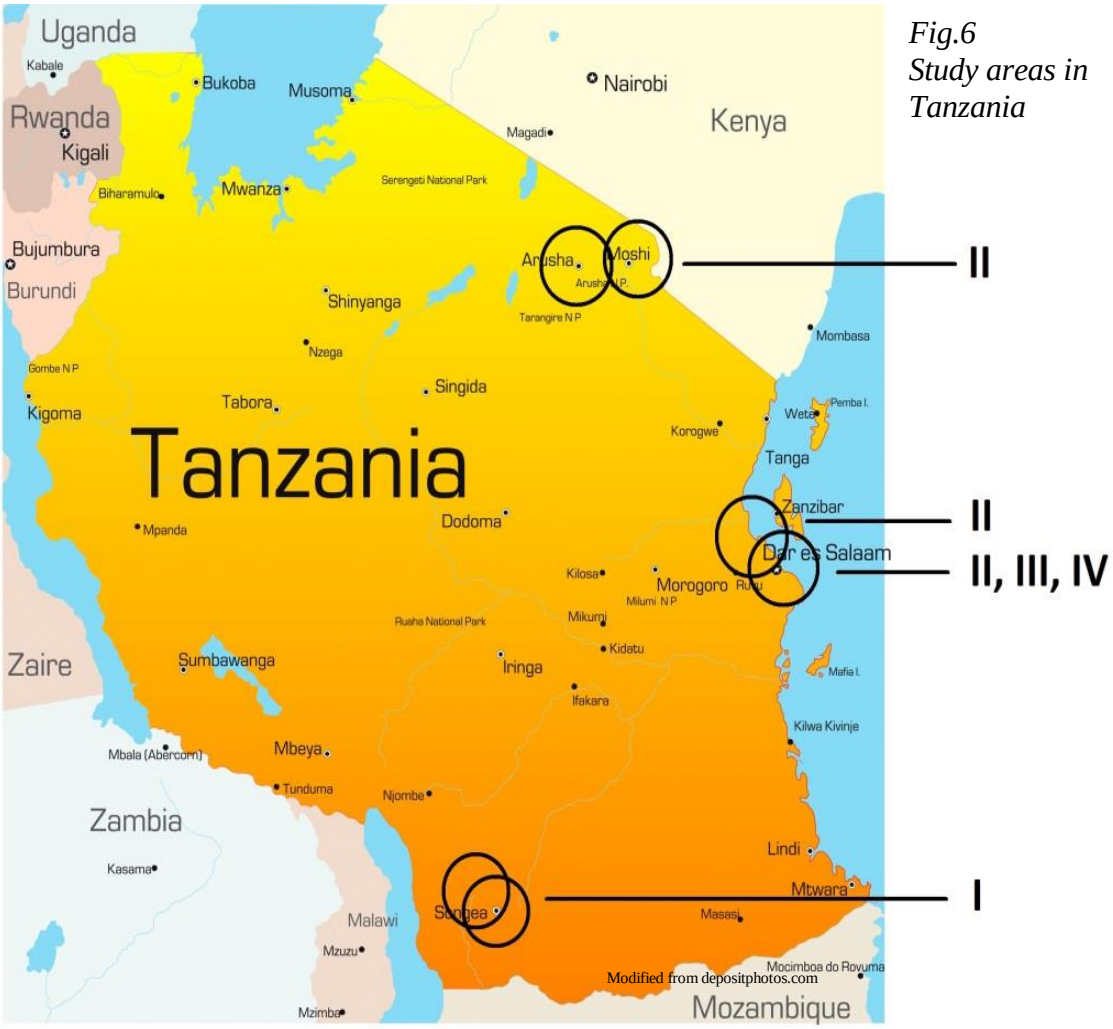


Fig.6
Study areas in Tanzania

Study 1 took place in two hospitals in South-west Tanzania: St Joseph's Hospital, Peramiho and Songea Regional Hospital (Fig. 6). The hospitals serve as first and second level referral centres for a largely rural population of an estimated 1 million people in Ruvuma Region. St. Joseph's Hospital, with 400 beds, is an NGO-run hospital in Peramiho. Songea Regional, with 350 beds, is a state-run regional hospital.

The survey in **Study II** was of ten hospitals in four regions of the country, serving a total population of 6.8 million (18% of the population of mainland Tanzania). Four are district hospitals, three are regional hospitals, two are referral hospitals and one is an NGO-run, private hospital.

Studies III and IV took place in Muhimbili National Hospital, the 1500-bedded referral hospital receiving patients from the Dar es Salaam area (approximately 4.5 million inhabitants) and from other hospitals throughout the country.

METHODS

Study	Title	Design	Study population	Study period	Number of subjects	Analysis
I	Use of an early warning score and ability to walk predicts mortality…	Cohort	All patients over 12 years old admitted to the medical departments in two hospitals	Oct - Nov 2005	709 patients	Logistic regression, predictive values, ROC curves
II	Emergency and critical care services in Tanzania…	Cross-sectional survey	10 hospitals in four regions	Oct - Nov 2009	10 hospitals	Descriptive statistics including calculation of resource availability scores
III	Single deranged physiologic parameters are associated with mortality…	Cohort	All adults cared for on the ICU in one university hospital	Nov 2012 - Mar 2014	269 patients	Multivariable logistic regression, chi-squared & Wilcoxon rank-sum tests
IV	Vital Signs Directed Therapy: Improving care…	Before-and-after interventional study	All adults cared for on the ICU in one university hospital	Nov 2012 - May 2015	447 patients	Multivariable regression models, chi-squared & Wilcoxon rank-sum tests

Table 2 Summary of the methods used in the four studies

STUDY I

Study I was a prospective, observational, cohort study of patients over 12 years old admitted to the medical departments in two Tanzanian hospitals during a two month period. Vital signs were measured at admission for 709 patients. After discharge or death, the patient notes were reviewed and an Early Warning Score – a compound score of blood pressure, pulse rate, respiratory rate, temperature and conscious level – was calculated. The association between in-hospital mortality and deranged vital signs, EWS and ability-to-walk was assessed and predictive values calculated.

STUDY II

Study II was a cross-sectional survey of ten hospitals in four regions in Tanzania to assess the facilities, availability of resources and routines for emergency and critical care. Quality was evaluated with standards developed using an expert group methodology. The proportion of hospitals where each resource was available and "resource availability scores" for each hospital were calculated with missing data excluded.

Standards for Emergency and Critical Care

The expert group comprised of the researchers plus international anaesthesiologists and physicians. Existing literature was reviewed and relevant standards were extracted from international guidelines for trauma, paediatrics, surgery and anaesthesia. The standards were revised via face-to-face meetings and email and telephone communication until consensus was reached. The standards (see Appendix) were divided into eight sections: infrastructure; human resources; training; drugs; equipment; routines; guidelines; and support services.

STUDY III

Study III was a prospective, observational, cohort study of 269 adults during a 15 month period on the ICU in Muhimbili National Hospital, Dar es Salaam. Photographs were taken of all the observation charts on the ICU every day and data on the vital signs at admission to the ICU were extracted to a database together with patient and admission characteristics. The patients were followed up on the wards until discharge or death. Cut-offs for deranged physiological parameters known as *danger signs* were defined a priori based on the Karolinska University Hospital's Medical Emergency Team protocol (Fig. 7). Their associations with in-hospital mortality were analysed and single parameter danger signs were compared to a compound scoring system.

Glasgow Coma Scale	3-8
Respiratory Rate / min	<8 or >30
Inspired Oxygen	80-100% or >10L/min
Oxygen Saturation	<90%
Heart Rate / min	<40 or >130
Systolic Blood Pressure	<90mmHg

Fig. 7 Danger signs in study III

STUDY IV

Study IV was a prospective, before-and-after interventional study of 447 patients on the ICU in Muhimbili National Hospital, Dar es Salaam in a 2 ½ year period. Data collection methods were the same as used in **Study III** and the pre-implementation patients were the **Study III** cohort. The intervention consisted of the use of the Vital Signs Directed Therapy (VSDT) Protocol, a context-appropriate protocol that specified actions when danger signs were identified (Fig. 8).

Acute treatments of danger signs were compared pre and post-implementation at admission to ICU for all patients. Acute treatments were also compared for every danger sign identified during care on the ICU in a sample of three months pre-implementation and three months post-implementation. In-hospital mortality rates pre and post-implementation were analysed.

Vital Signs Directed Therapy

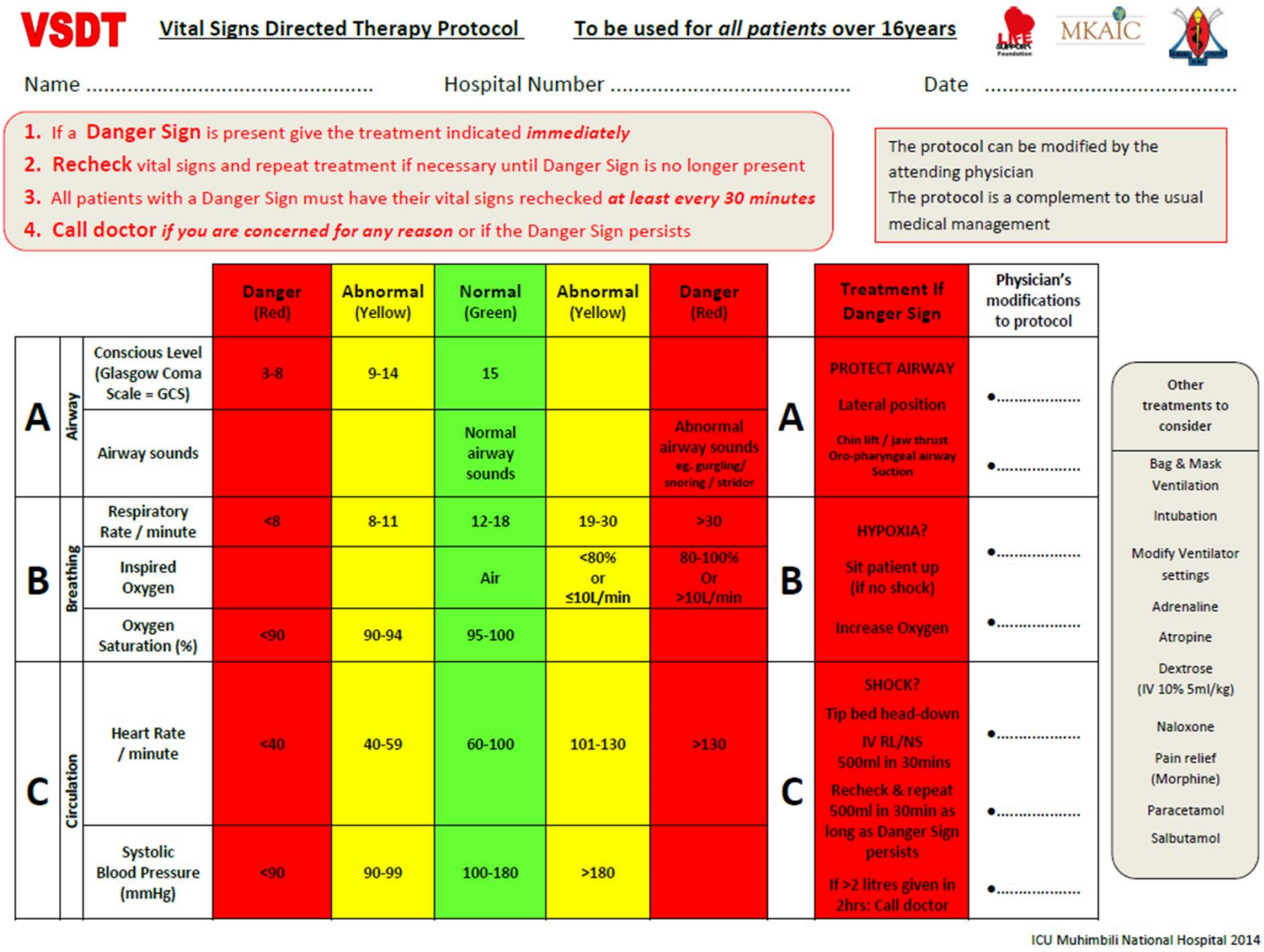
A protocol was required that fulfilled the following criteria: (i) be feasible given the time and resource constraints in a low resource setting; (ii) include specified treatments that nurses can give without a physician's immediate presence; (iii) be modifiable by treating physicians; and (iv) include prompts for more advanced therapies. Previously described protocols for Early Warning Scores and Rapid Response Systems did not satisfy these criteria and so the VSDT protocol was developed. A first draft of the protocol including the danger sign cut-offs used in **Study III** was compiled by the researchers. An expert group (the researchers, ICU nurses and physicians from Karolinska and Muhimbili, and two further experts in critical care in low-income countries) iteratively revised the protocol via face-to-face meetings and email and telephone communication until consensus was reached.

Implementation of VSDT

Implementation of the VSDT protocol was multi-faceted and conducted in a four week period in Muhimbili. Standard operating procedures requiring the use of the protocol were written and signed by the hospital administration and head of department. All ICU nurses and doctors were trained in formal sessions in the hospital, and learning was reinforced with bedside teaching. Clinicians in the other departments in the hospital and in the adjacent university were informed about the protocol at several sensitisation meetings and seminars. Large posters of the protocol were put up on the walls of the ICU. Two doctors and four nurses were designated as local facilitators and received extra training to be able to reinforce the use of the protocol during the post-implementation period. The protocol was attached to the patients' observation charts daily post- implementation. Following the implementation, regular communication between the research teams in Sweden and Tanzania facilitated logistics and allowed feedback on performance and outcomes. Four short supervisory visits by members of the Swedish team were conducted post- implementation period.

STATISTICAL ANALYSIS

Stata (Release 12, StataCorp, Texas) and SPSS (v15, SPSS Inc., Chicago, USA) statistical software were used. P-values <0.05 were considered statistically significant and 95% confidence intervals were stated when appropriate. Data were summarized with mean, median, range and inter-quartile ranges for numerical variables, and frequency tables for categorical variables. Bivariate analyses used chi-squared test for categorical variables and t-test or Wilcoxon rank sum test for numerical variables. Logistic regression was used for associations with mortality and other binary outcomes. Multivariable models were built in **Studies I, III** & **IV**. In **Study IV**, generalized linear models were used to provide prevalence ratios which are more intuitively interpretable than odds ratios. For analyses including multiple data points from the same patient (clustered data), mixed-effects models and generalised estimating equations were used. To estimate predictive values of vital signs, receiver operating characteristic curves were generated in **Studies I** and **III**.



VSDT Vital Signs Directed Therapy Protocol — To be used for *all patients* over 16years

Name ..... Hospital Number ..... Date .....

1. If a **Danger Sign** is present give the treatment indicated ***immediately***
2. **Recheck** vital signs and repeat treatment if necessary until Danger Sign is no longer present
3. All patients with a Danger Sign must have their vital signs rechecked ***at least every 30 minutes***
4. **Call doctor** ***if you are concerned for any reason*** or if the Danger Sign persists

The protocol can be modified by the attending physician
The protocol is a complement to the usual medical management

			Danger (Red)	Abnormal (Yellow)	Normal (Green)	Abnormal (Yellow)	Danger (Red)		Treatment If Danger Sign	Physician's modifications to protocol
A	Airway	Conscious Level (Glasgow Coma Scale = GCS)	3-8	9-14	15			A	PROTECT AIRWAY Lateral position Chin lift / jaw thrust Oro-pharyngeal airway Suction	•..... •.....
		Airway sounds			Normal airway sounds		Abnormal airway sounds eg. gurgling/ snoring / stridor			
B	Breathing	Respiratory Rate / minute	<8	8-11	12-18	19-30	>30	B	HYPOXIA? Sit patient up (if no shock) Increase Oxygen	•..... •.....
		Inspired Oxygen			Air	<80% or ≤10L/min	80-100% Or >10L/min			
		Oxygen Saturation (%)	<90	90-94	95-100					
C	Circulation	Heart Rate / minute	<40	40-59	60-100	101-130	>130	C	SHOCK? Tip bed head-down IV RL/NS 500ml in 30mins Recheck & repeat 500ml in 30min as long as Danger Sign persists If >2 litres given in 2hrs: Call doctor	•..... •..... •.....
		Systolic Blood Pressure (mmHg)	<90	90-99	100-180	>180				

Other treatments to consider

Bag & Mask Ventilation
Intubation
Modify Ventilator settings
Adrenaline
Atropine
Dextrose (IV 10% 5ml/kg)
Naloxone
Pain relief (Morphine)
Paracetamol
Salbutamol

ICU Muhimbili National Hospital 2014

Fig.8 Vital Signs Directed Therapy Protocol
As used in Study IV

ETHICAL CONSIDERATIONS

All the research in this thesis has been conducted in accordance with strict ethical principles. Ethical clearance for each study was approved by the relevant ethical committees and local authorities. The issues below were of particular consideration.

Benefit vs. Risk

Medical research is ethical only if the benefits outweigh the risks (96). The potential benefits of researching improvements to the quality of critical care in low resource settings were substantial. Results could lead to reduced mortality and morbidity, both for the subjects studied and for future patients. Potential risks included harmful treatments to individual patients and breaches of confidentiality. For each study these considerations were evaluated and it was adjudged by the researchers, the local health staff and the ethical committees that the benefits outweighed the risks.

Confidentiality and consent

All data that could be traced to individual patients in **Studies I, III** and **IV** were removed before final analysis and reporting. Informed consent from patients was not possible due to their critical illness and the service-wide quality improvement nature of the studies. Information about the identity of the health staff interviewed in **Studies II** and **IV** was kept confidential and removed before reporting. Consent was sought from all interviewees and they were informed that they could withdraw from the research at any time. Data were stored on secure, institutional servers.

International Research

It was seen as essential that the studies would assist in building research capacity in Tanzania. All the studies were conducted as collaborations between institutions and researchers in Tanzania and Sweden (and the UK in **Study I**). The principal investigators and co-authors for all studies came from both countries, and all were involved in study design, data collection, analysis and write-up. Moreover, **Studies II-IV** were embedded within the long-term, ongoing MKAIC collaboration which aims to build capacity and improve services.

Ethics of observing critical care processes

A particular ethical challenge in critical care arises when studying the process of care. If a researcher observes poor quality care, is she/he obliged to intervene? This challenge precluded study designs involving direct observation by researchers trained as critical care doctors or nurses. Instead, processes of care were evaluated in **Study IV** by analysing the care that had been documented on the patient observation charts.

RESULTS

STUDY I

Use of an early warning score and ability to walk predicts mortality in medical patients admitted to hospitals in Tanzania

77 of the 709 patients died in-hospital (10.8%). Vital signs at admission to hospital by EWS category and their association with mortality are shown in Table 3. Low blood pressure was associated with mortality (increasing from odds ratio (OR) 2.1 for mild hypotension to OR 6.3 for severe hypotension). Tachycardia (pulse rate >130) was associated with mortality (OR 2.6). Decreasing levels of consciousness were associated with mortality (OR 3.0 – 10.0).

EWS component score[a]	**3**	**2**	**1**	**0**	**1**	**2**	**3**
Systolic BP	**≤70**	**71-80**	**81-100**	**101-199**		**≥200**	
OR (95% CI)	6.3 (2.9.13.7)	2.9 (1.2-7.0)	2.1 (1.2-3.6)			2.6 (0.6-12.4)	
Pulse rate		**≤40**	**41-50**	**51-100**	**101-110**	**111-129**	**≥130**
OR (95% CI)		3.5 (0.4-34.7)	1.8 (0.2-15.0)		1.6 (0.8-3.2)	1.0 (0.5-2.1)	2.6 (1.3-5.0)
Respiratory rate		**<9**		**9-14**	**15-20**	**21-29**	**≥30**
OR (95% CI)		NA			0.6 (0.1-5.3)	0.6 (0-1-5.4)	1.7 (0.2-14.6)
Temperature		**<35**		**35-38.4**		**≥38.5**	
OR (95% CI)		1.8 (0.4-8.3)				0.7 (0.2-2.4)	
Conscious Level (AVPU)				**Alert**	**Verbal**	**Pain**	**Unresponsive**
OR (95% CI)					3.0 (1.3-6.8)	3.1 (1.1-8.8)	10.0 (2.8-35.5)

Table 3 Odds ratio of death by physiological parameters

EWS Early warning score indicates the grade of derangement from normal for each observation: summing these over the 5 categories gives the total EWS
BP blood pressure OR odds ratio NA not available AVPU Alert Verbal Pain Unresponsive

The risk of dying increased as the compound EWS increased (Fig. 9). A patient with a critical EWS score of 5 or more had 2.9 times the odds of dying compared with a patient with a normal score of 0 or 1 (95% CI 1.8 – 4.9). Inability to walk had a strong association with mortality OR 6.5 (95% CI 3.3—12.9)

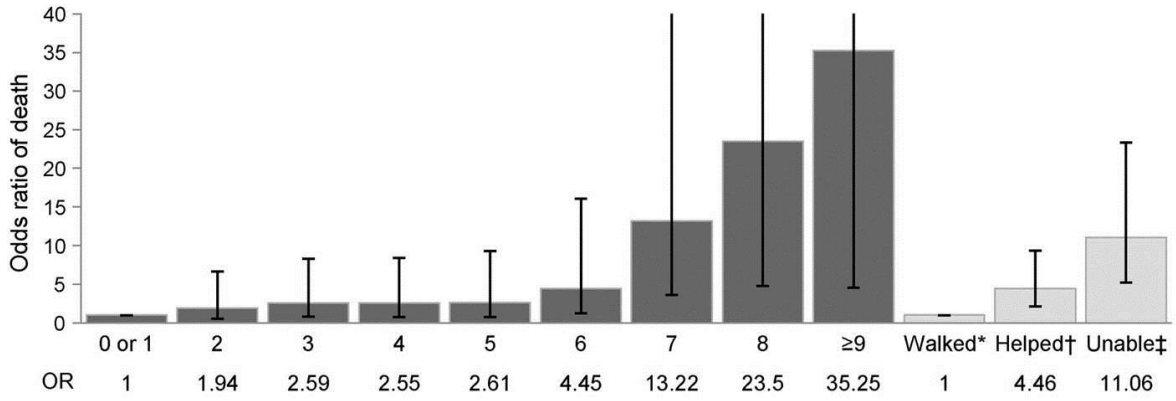


Fig. 9 Odds ratios (OR) of death according to patient early warning score and walking status on admission (dark grey and light grey bars, respectively)

STUDY II

Emergency and critical care services in Tanzania: a survey of ten hospitals

The characteristics of the ten hospitals in Tanzania that were studied can be seen in Table 4.

	Hospital									
	1	2	3	4	5	6	7	8	9	10
Type	District	District	District	District	Regional	Regional	Regional	Referral	Private	Referral
Number of beds	<200	200-400	200-400	200-400	>400	200-400	200-400	>400	<200	>400
Number of specialist doctors (excluding anaesthesiologists)	2	6	6	8	7	1	5	>50	18	25
Number of specialist anaesthesiologists	0	0	0	0	0	0	0	6	0	1
Number of non-specialist clinician anaesthetists	0	3	3	1	1	3	3	12	0	4
ICU	No	No	No	No	No	No	No	Yes	Yes	Yes
Number of operating theatres	1	n/a	2	2	5	2	1	11	n/a	9

Table 4 Hospital Characteristics

ICU Intensive Care Unit n/a not available

Resource Availability Scores

The median Resource Availability Score was 71.1% (range 57.1% to 92.1%), calculated as the percentage of resources available in each hospital, missing data excluded. The referral/private hospitals had higher scores than district/regional hospitals (89.7% vs 70.6%). Scores for routines (42.2%) and for infrastructure (50.0%) were lower than drugs (100%) and equipment (90.0%) (Fig. 10).

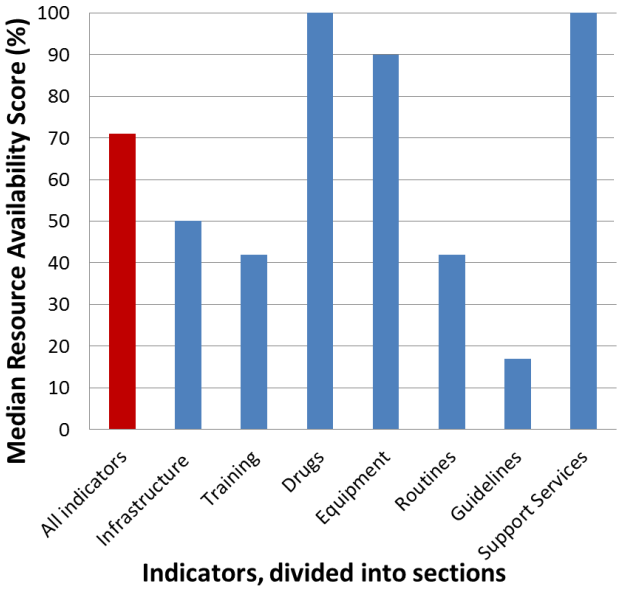


Fig. 10 Emergency and critical care resource availability scores in ten hospitals in Tanzania

Human Resources not included due to missing data

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Infrastructure

Less than one-third of the hospitals had an emergency room - the general outpatients department or the inpatient wards were used for emergency patients. None of the district or regional hospitals had an adult triage area or intensive care unit.

Human Resources and Training

The two referral hospitals had specialist Anaesthesiologists. Associate clinicians or nurses provided anaesthesia in the other hospitals. None of the hospitals could satisfy the standard of having all relevant staff trained in triage, emergency care or critical care. Two hospitals had at least one staff trained in adult triage or critical care and three hospitals had at least one staff trained in WHO's paediatric Emergency Triage & Treatment (ETAT).

Drugs and Equipment

Intravenous fluids, parenteral opioids, diazepam, antibiotics, blood pressure cuffs, naso-gastric tubes, suction machines and gloves were available in all hospitals. Oxygen was available in nine of the hospitals. Half of the hospitals had backup electricity generator. The smaller district and regional hospitals had slightly less availability of drugs and equipment than the larger referral and private hospitals (86.7% vs 100%).

Routines and Written Guidelines

There were formal systems of triage for adults in 40% of hospitals and systems for prioritising the management of critically ill adults in 44%. There were routines for delaying registration and payment until after triage and emergency treatment at all hospitals for children and all except one for adults. Eighty-three percent of hospitals had routines for increasing the frequency of observations for critically ill adults. However, clinician ward rounds for critically ill patients were carried out more than once daily in only 30% of

hospitals. None of the district or regional hospitals had written guidelines for adult triage, emergency treatment or critical care.

Support Services

Facilities for checking haemoglobin, conducting bacterial gram stain, and performing chest x-rays were available in all hospitals. Eighty percent of hospitals could perform bacterial cultures and sensitivities and 90% could measure serum electrolytes. Emergency blood transfusions were available in all hospitals and in 80% this could be done within one hour of receiving a blood-group specimen.

Advanced Emergency and Critical Care

Four of the ten hospitals had mechanical ventilators. Arterial blood gas monitoring was present in two hospitals and central venous pressure monitoring in one. Twenty-five percent of all indicators were available across all hospitals, with more (80%) in referral/private hospitals than in district/regional hospitals (20%).

STUDY III

Single deranged physiologic parameters are associated with mortality in a low-income country

The average age of the 269 patients was 35 years (range 16-85) and 54% were female. Twenty-six percent were planned admissions after elective surgery – three-quarters of these were still intubated but were not treated with mechanical ventilation (delayed extubation). Forty-two percent of the patients were admitted following emergency surgery and the remaining 32% were medical patients.

Illness Severity

Sixty-nine percent of patients had one or more danger signs at admission to ICU. The patients had an average of 1.3 (range 0-5) danger signs. The median length-of-stay on the ICU was 1.8 days (30minutes – 66 days) and mortality on ICU was 44%. In-hospital mortality was 50%. The patients who had planned admissions had fewer danger signs, shorter length-of-stay and a lower in-hospital mortality rate than the unplanned admissions (Table 5).

			All n=269	Planned admissions n=69	Unplanned admissions n=200	p
Danger signs	Patients without any danger signs	n (%)	83 (31%)	49 (71%)	34 (17%)	<0.001[a]
	Patients with one or more danger sign	n (%)	186 (69%)	20 (29%)	166 (83%)	
	Number of danger signs	Mean (Range)	1.3 (0-5)	0.3 (0-3)	1.6 (0-5)	<0.001[b]
NEWS	Patients with NEWS <7	n (%)	101 (38%)	43 (62%)	58 (29%)	<0.001[a]
	Patients with NEWS ≥ 7	n (%)	168 (62%)	26 (38%)	142 (71%)	
	NEWS	Mean (Range)	7.8 (0-18)	6.1 (0-12)	8.3 (0-18)	<0.001[b]
Mortality rates	24-hour mortality	n (%)	39 (14%)	1 (1%)	38 (19%)	<0.001[a]
	ICU mortality	n (%)	119 (44%)	3 (4%)	116 (58%)	<0.001[a]
	In-hospital mortality	n (%)	134 (50%)	5 (7%)	129 (65%)	<0.001[a]
	Length of Stay on ICU	Median (Range in days)	1.8 (0.02-66)	0.9 (0.7-15)	2.7 (0.02-66)	<0.001[b]

Table 5 Illness severity at admission, mortality rates and length-of-stay

Illness severity at admission by danger signs and NEWS score; mortality rates and length-of-stay on the ICU, grouped into planned and unplanned admissions
p-values compare groupings by [a] chi squared for proportions and [b] Wilcoxon rank-sum for non-parametric data
NEWS National Early Warning Score ICU Intensive Care Unit

Danger signs as prognostic factors for mortality

In-hospital mortality rates by the number of danger signs, heart rate and systolic blood pressure can be seen in Fig. 11. The in-hospital mortality rate for patients with one or more danger sign was 64%, compared to 18% without (p<0.001). The presence of a danger sign at admission had a positive association with mortality (adjusted Odds Ratio (OR) 4.6 (95% CI 2.0-11.1 p<0.001) (Table 6). Mortality increased as the number of danger signs increased (adjusted OR per increase of one danger sign 2.2 (1.5-3.3) p<0.001).

Each individual danger sign was associated with mortality with statistically significant unadjusted ORs between 1.9 and 16.2 (Table 6). Danger signs for Glasgow Coma Scale (GCS), respiratory rate and systolic blood pressure remained significant after adjusting. Systolic blood pressure less than 90 mmHg had the strongest association (OR 16.2 (4.8-54.0)). Severe hypothermia (body temperature ≤35.1 °C) (OR 0.3 (0.0-2.6) p=0.28), severe hyperthermia (body temperature ≥39.1°C) (OR 1.0 (0.4-2.7) p=0.85), and hypertension (systolic blood pressure >180) (OR 0.7 (0.1-7.5) p=0.74), were not associated with mortality.

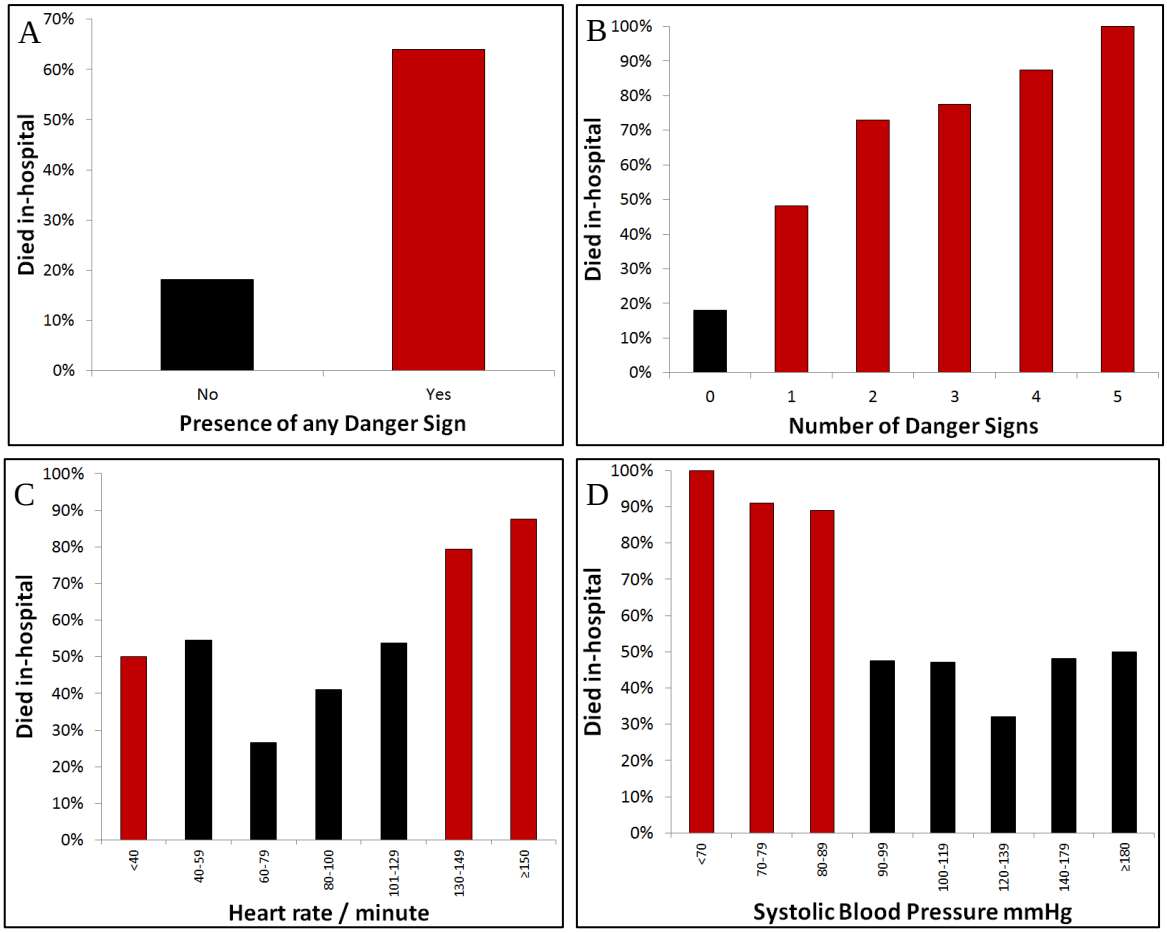

*Fig. 11 In-hospital mortality rates by presence of a danger sign (**A**), number of danger signs (**B**), heart rate (**C**), and systolic blood pressure (**D**) at admission*

Missing vital signs excluded from graphs. Red bars represent danger signs and black bars represent normal

Other factors and mortality

Increasing age was associated with mortality – adjusted OR 1.03 per year (1.01-1.06) p=0.003, but gender was not (OR 0.7 (0.4-1.5) p=0-16). The use of mechanical ventilation at admission was associated with mortality (adjusted OR 3.5 (1.2-10.4) p=0.03) and a critical NEWS score of ≥7 had an association with mortality (adjusted OR 2.5 (1.2-5.1) p=0.01).

Physiological Derangement	In-hospital Mortality				Odds ratios (95% CI)	
	Without the derangement		With the derangement		Unadjusted	Adjusted
	n^1/n^2	%	n^1/n^2	%		
One or more deranged physiological parameter	15/83	18.0%	119/186	64.0%**[a]	8.1 (4.3-15.2)**	4.6 (2.0-11.1)**[b]
NEWS ≥ 7	32/101	31.7%	102/168	60.7%**[a]	3.3 (2.0-5.6)**	2.5 (1.2-5.1)*[b]
Conscious Level (GCS ≤ 8)	43/132	32.6%	91/137	66.4%**[a]	4.1 (2.5-6.8)**	2.3 (1.0-5.0)*[c]
Respiratory Rate (< 8 or > 30 / min)	95/214	44.4%	39/55	70.9%**[a]	3.1 (1.6-5.8)*	3.0 (1.1-8.0)*[c]
Inspired Oxygen (≥ 80% or ≥ 10L/min)	99/213	46.5%	35/56	62.5%*[a]	1.9 (1.1-3.5)*	0.8 (0.3-2.3)[c]
Oxygen Saturation (<90%)	114/242	47.1%	20/27	74.1%*[a]	3.2 (1.3-7.9)*	1.5 (0.4-5.4)[c]
Heart Rate (<40 or >130 / min)	104/232	44.8%	30/37	81.1%**[a]	5.3 (2.2-12.5)**	2.0 (0.7-6.2)[c]
Systolic Blood Pressure (<90 mmHg)	98/230	42.6%	36/39	92.3%**[a]	16.2 (4.8-54.0)**	32.6 (7.0-151.0)**[c]

Table 6 Mortality and association with physiological derangements at admission

In-hospital mortality and associations with physiological derangements at admission expressed as the presence of a danger sign, a critical NEWS score and each individual danger sign

CI Confidence Intervals NEWS National Early Warning Score GCS Glasgow Coma Scale
n^1 number of patients that died n^2 number of patients
** p<0.05 ** p<0.001*
[a] chi-squared
odds ratios calculated with unadjusted and multivariable logistic regression
[b] Adjustments for age, admitting specialty, admitting ward, intubation and mechanical ventilation
[c] Adjustments for age, admitting specialty, admitting ward, intubation and mechanical ventilation and all other individual danger signs

STUDY IV

Vital Signs Directed Therapy: Improving care on an Intensive Care Unit in a low-income country

Of the 447 included patients, 269 were pre-implementation and 178 post-implementation. The post-implementation patients were older than the pre-implementation patients, but other baseline characteristics and illness severity were similar.

Danger signs

At admission, 70% of pre-implementation and 66% of post-implementation patients had one or more danger sign. Overall, danger signs for respiratory rate (38%), heart rate (37%) and systolic blood pressure (20%) were the most common. Conscious level (3%) and oxygen saturation (2%) danger signs were less common.

Acute-treatments

At admission, acute treatments of all danger signs increased after the implementation (72.9% vs 23.1%, Prevalence Ratio (PR) 3.2 (CI 2.2-4.5)) (Table 7). An increase in acute treatments was seen for each individual danger sign. The largest increase at admission was for low systolic blood pressure: 80.0% of hypotensive patients received intravenous fluids post-implementation, compared to 36.1% pre-implementation (PR 2.2 (1.4-3.5)).

In the six sample months used for analysing care during the patients' stay on ICU, acute treatments of all danger signs also increased after the implementation (16.6% vs 2.9% (PR 4.9 (2.9-8.3)). Again, the largest increase was for low systolic blood pressure: 35.0% of patients received an acute treatment of intravenous fluid post-implementation, compared to 4.1% pre-implementation (PR 6.4 (2.5-16.2)). Fig. 12 illustrates that the increase in acute treatments occurred at the same time point as the implementation of the VSDT protocol.

		Acute treatments					**Adjusted[1] Odds Ratio** (95% CI)		**Adjusted[1] Prevalence Ratio** (95% CI)	
		pre-implementation		**post-implementation**						
		n/n_{tot}	%	n/n_{tot}	%	p-value				
At admission	**All Danger Signs**	**36/156**	**23.1**	**62/85**	**72.9**	**<0.001**	**9.2[2]**	**(4.9-16.5)**	**3.2[3]**	**(2.2-4.5)**
	GCS<9	4/22	18.2	8/11	72.7	0.002	10.6[4]	(1.8-61.5)	4.0[5]	(1.5-10.4)
	Respiratory Rate <8 or >30 / minute	3/47	6.4	8/17	47.1	<0.001	14.8[4]	(3.1-70.9)	7.8[5]	(2.4-25.8)
	Oxygen Saturation <90%	9/23	39.1	12/14	85.7	0.006	10.5[4]	(1.8-62.2)	2.2[5]	(1.3-3.8)
	Heart Rate <40 or >130 beats/ minute	7/28	25.0	13/17	76.5	0.001	9.9[4]	(2.4-41.1)	3.1[5]	(1.5-6.1)
	Systolic Blood Pressure <90 mmHg	13/36	36.1	21/26	80.0	<0.001	7.6[4]	(2.3-25.4)	2.2[5]	(1.4-3.5)
During care on ICU	**All Danger Signs**	**38/1304**	**2.9**	**216/1299**	**16.6**	**<0.001**	**3.7[2]**	**(1.7-8.0)**	**4.9[3]**	**(2.9-8.3)**
	GCS<9	3/78	3.9	0/0	-	-	-	-	-	-
	Respiratory Rate <8 or >30 / minute	4/561	0.7	11/419	2.6	0.016	4.0[2]	(1.2-12.8)	4.1[3]	(1.3-12.6)
	Oxygen Saturation <90%	0/17	0.0	4/25	16.0	0.083	-	-	-	-
	Heart Rate <40 or >130 beats/min	22/426	5.2	94/549	17.1	<0.001	4.2[2]	(1.7-10.0)	2.7[3]	(1.5-4.8)
	Systolic Blood Pressure <90 mmHg	9/222	4.1	107/306	35.0	<0.001	14.5[2]	(5.0-42.4)	6.4[3]	(2.5-16.2)

Table 7 Acute treatments carried out when danger signs detected at admission to the ICU and during care on the ICU pre and post implementation

[1] Odds ratios and prevalence ratios adjusted for age
[2] Odds ratios calculated with mixed-effects models when data were clustered within patients
[3] Prevalence Ratios calculated with generalised estimating equations when data were clustered within patients
[4] Odds ratios calculated with logistic regression
[5] Prevalence Ratios calculated with generalised linear models
n/n_{tot} number of times protocol adhered to divided by number of danger signs ICU Intensive Care Unit GCS Glasgow Coma Score

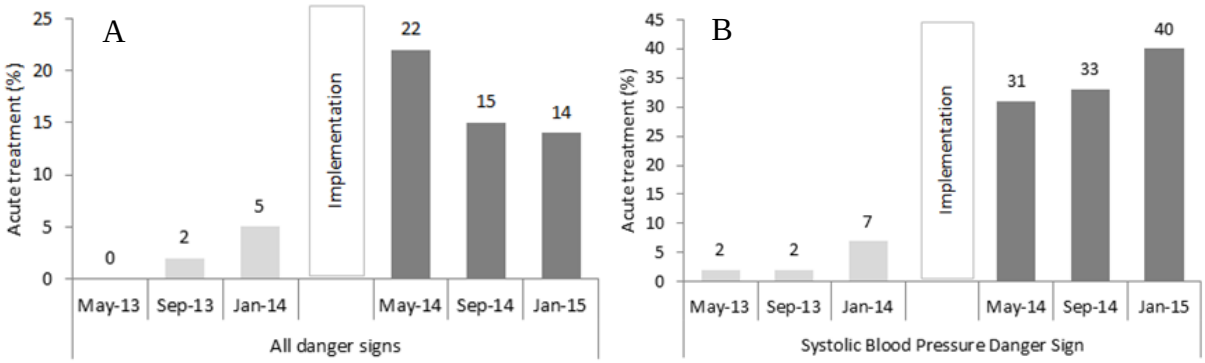

Fig. 12 Acute treatments in each sampled month for all danger signs (A) and systolic blood pressure (B)

Mortality

Overall in-hospital mortality rates did not change (49.4% post-implementation vs 49.8% pre-implementation, p=0.94) (Table 8). For patients admitted with low systolic blood pressure, mortality was lower post-implementation (69.2% vs 92.3%, p=0.02). To prevent the death of one patient admitted with hypotension, the number-needed-to-treat with VSDT was 4.3.

	In-hospital mortality								
	pre-implementation		**post-implementation**						
	n/n_{tot}	%	n/n_{tot}	%	**p-value**[1]	**Adjusted Odds Ratio**[2] (95% CI)		**Adjusted Prevalence Ratio**[3] (95% CI)	
All patients	**135/269**	**49.8**	**88/178**	**49.4**	**0.94**	**1.1**	**(0.7-1.6)**	**1.1**	**(0-9-1.3)**
One or more Danger Sign	119/187	63.6	72/117	61.5	0.71	1.1	(0.7-1.9)	1.1	(0.9-1.3)
Heart rate Danger Sign	30/37	81.1	12/17	70.6	0.39	1.8	(0.5-6.7)	1.2	(0.8-1.7)
Systolic Blood Pressure Danger Sign	36/39	92.3	18/26	69.2	0.02	5.3	(1.3-22.5)	1.3	(1.02-1.7)
Unplanned admissions	**129/200**	**64.5**	**84/139**	**60.4**	**0.45**	**1.3**	**(0.8-2.0)**	**1.1**	**(0.9-1.3)**

Table 8 In-hospital mortality in pre and post-implementation patients, by the presence of danger signs at admission

n/n_{tot} number of deaths divided by number of patients
[1] chi2
[2] odds ratios calculated by logistic regression, adjusted for age
[3] prevalence ratios calculated by generalised linear models adjusted for age

DISCUSSION

METHODOLOGICAL CONSIDERATIONS

QUALITY ASSESSMENT

The first aim of this thesis was to assess the quality of critical care in low resource settings. Understanding current quality of care is a necessary first step to make improvements. Donabedian in 1978 constructed a model for assessing quality based on structure (physical and human resources, training levels, organisation), process (how the care is delivered), and outcomes (changes in health status) (97). In this thesis, **Study II** evaluates the structure, **Study IV** the processes and **Studies III** and **IV** the outcomes of critical care.

Measuring quality

To measure quality, a definition of good quality is required (98). In each medical field and for each level of resources, standards are developed to provide such definitions, for example for intravenous fluid therapy in the UK (99) and for safe anaesthesia globally (100). Standards are often written by an expert group who reach a consensus following several rounds of meetings or communications (101). The standards should be based on the best available evidence which in low resource settings is challenging due to the paucity of research. The standards developed in **Study II** (see Appendix) used an expert group methodology with a limited underlying evidence base, and without the possibility of validation. The ongoing aim is for the standards to be refined as better evidence accumulates. In **Study IV** an expert group was also used to design the VSDT protocol.

Know-do gap

Improving quality can either involve discovering new and better ways of treating patients, or by ensuring that existing knowledge is utilised effectively. Effective coverage of medical interventions that are known to work to all people who need them is the central goal of global health (102). The "know-do gap" describes situations whereby knowledge exists but is not translated into practice. Although present worldwide, this gap is greatest in low resource settings. Often the know-do gap resulting in poor quality care is a larger bottleneck to achieving effective coverage than the patients' access to health facilities (95). As one author emphasises "We need to prioritize both access and quality, because doing more isn't better. Doing better is better" (103). The VSDT protocol used in **Study IV** was an attempt to close a know-do gap – the acute treatments are known to be effective and the protocol aimed to translate the knowledge into action.

Outcomes

In **Studies I, III** and **IV**, in-hospital mortality was used as an outcome measure. This outcome was chosen as it was adjudged of greater interest to the patient than either the briefer measure of ICU-mortality or of time-to-death within the stay in hospital. A limitation was

potential misclassification of terminally ill patients who were taken home to die, but 30 or 90 day follow-up post discharge was not possible in the study settings.

ASSOCIATION AND PREDICTION

The thesis' second aim was to investigate the association between deranged vital signs and mortality. The objectives were to understand the information that deranged vital signs provide about subsequent outcomes, and whether it may be reasonable to target an intervention at normalising derangements. This required an understanding of several epidemiological concepts described below.

Prevalence and Incidence

Epidemiology is the study of disease occurrence in populations (104). Often, the relationships between people's **characteristics**, (e.g. gender or exposure to tobacco), and **outcomes**, (e.g. onset of disease or death), are studied. A characteristic and an outcome are **associated** if they are statistically dependent – ie as the presence of the characteristic varies, so does the outcome. The **proportion** of a population with an outcome can be described using prevalence or incidence. **Prevalence** is the proportion at a given *point* in time, while **incidence** is the proportion that develop the outcome over a given *period* of time. Prevalence is usually expressed as a percentage, while incidence is expressed as a percentage per time unit, for example percentage per year.

The use of prevalence or incidence depends on the study design: **cross-sectional** studies that look at people at a single point in time use prevalence, while **longitudinal** studies that follow people over time use incidence. **Risk** in epidemiology is the probability of a negative event occurring over a given point of time – ie the incidence. For example, the *risk* for a smoker of dying from lung cancer is 0.3% per year (104). **Study II**, a survey conducted at one point in time, had a cross-sectional design. In the cohort studies **I, III** and **IV** that followed patients until discharge or death, data about the *time* of discharge/death were not collected, precluding the use of incidence or risk.

Risk factors

A **risk factor** is a characteristic that is associated with a negative outcome. Risk factors are usually studied in healthy people where the outcome is onset of a disease. **Prognostic factors** are analogous to risk factors but are characteristics in diseased people and the outcome is an event connected to the disease. To use an example from this thesis – *hypotension* is a prognostic factor for the outcome of in-hospital death.

Causality

Establishing causality is a central goal for epidemiology and public health (105). A **cause** is a characteristic that results in an outcome. Causes can be **necessary** (needed to produce the

outcome), **sufficient** (inevitably produces the outcome), neither or both. Risk factors and prognostic factors can be causes, or they can be **markers** of another cause. Markers are associated with the outcome but are not causal. The association is due to a link with another characteristic, known as a **confounder**.

In order to study the relationship between a risk factor and an outcome, various statistical methods can be used including **multivariable regression models** (used in **Studies I, III** and **IV**). Such models keep the effects of other factors constant, and any remaining association is related to the factor of interest. However, most statistical models have the weakness that they can only include known factors – unknown confounders will be neglected which may lead to a false conclusion of causation instead of association. Furthermore, establishing causality is more than just a statistical task, and requires that several criteria are fulfilled, including temporality (the cause precedes the outcome) and biological plausibility (105).

It has been argued that causation is only interesting to public health practitioners when it is possible to design **interventions** that target the cause and improve health outcomes (106). The VSDT protocol in **Study IV** was such an intervention.

Continuing the example – **Studies I** and **III** found that *hypotension* was associated with mortality, but was it a marker or a cause? In both studies the association remained when known confounders were entered into a multivariable regression model and in **Study IV** treating the hypotension improved outcomes, providing some evidence that hypotension is a cause of death. In addition, the temporality criterion is satisfied, and causation is biologically plausible. However, it is also likely to be a marker for critical illness in general when death is due to other causes, which is illustrated in Fig. 13.

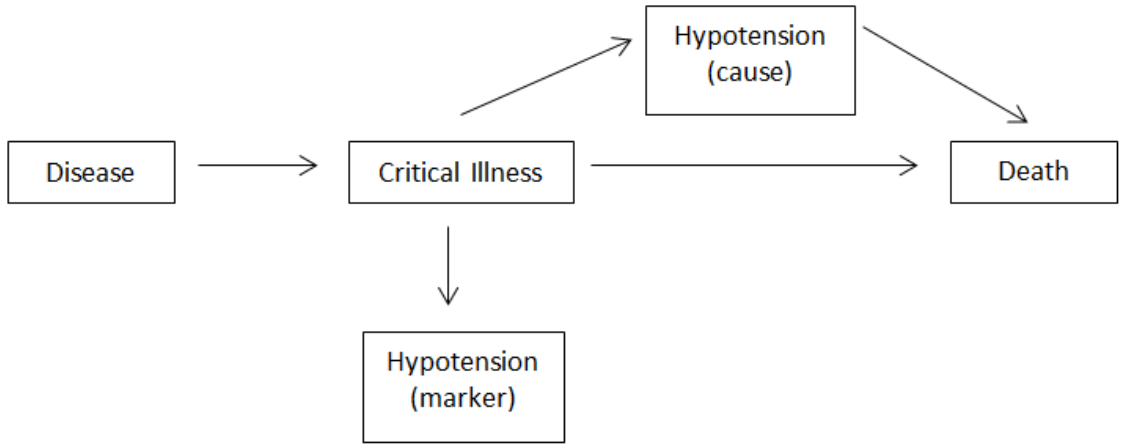

Fig. 13 The relationship between critical illness, hypotension and death

Relative risk

Relative risk compares the outcomes between groups with and without a risk factor. As a *risk*, it uses incidence, requiring a longitudinal study design and a given period of time. An

odds ratio is often used in epidemiology to estimate relative risk when the risk in the groups studied are not known (e.g. in cross-sectional or case-control studies). Odds ratios give a good approximation of relative risk if the outcome is rare (less than 1-5% (104)). Odds ratios have been criticised as they give an overly optimistic impression of the risk and are difficult to interpret – i.e. it is hard to have an intuitive understanding of an odds ratio of 3 (107-109).

In cross-sectional studies **prevalence ratios** can be used to estimate relative risks, comparing the prevalence in groups with and without a risk factor. Although they are not as commonly used as odds ratios, they provide a more conservative and interpretable measure for cross-sectional studies – a prevalence ratio of 3 implies that the probability is 3 times greater (108,109), and they were preferred in **Study IV**. To provide prevalence ratios, **generalised linear models** were used instead of logistic regression.

Prediction

Epidemiology pools individuals with the same risk factors to investigate associations with outcomes. The conclusions are averages at a population level, and are not aimed at **predicting** the outcome for an individual. For example, smoking has been found to be a risk factor for lung cancer, but it is not possible to predict that a smoker will get lung cancer – some smokers live long and healthy lives. **Clinical epidemiology** makes predictions about individual patients based on their risk and prognostic factors using epidemiological principles (104). The term **predictor** is used in clinical epidemiology for risk or prognostic factors in an individual.

Due to the complexity of causation and the variability between patients and pathologies, single predictors are unlikely to be adequately accurate (110) - even a strong predictor with a relative odds of 200 will misclassify the outcomes of many individuals (107). Predictors can be used to stratify individuals into risk groups, which while not able to determine outcome do facilitate clinical decisions. It is useful for a doctor to know which factors are predictors for poor outcome, whether the predictors are causal, and whether removing or treating the predictor improves the patient's outcome.

Predictive value

There are various ways of measuring a predictor's accuracy. In **Study I** sensitivity, specificity, receiver operator characteristic (ROC) curves and predictive values were used. **Sensitivity** is the proportion of people with the disease that have the predictor and **specificity** is the proportion without the disease that do not have the predictor For predictors that can take several values, choosing the cut-off value is a trade-off between sensitivity and specificity. Choosing a value with high sensitivity but low specificity will result in false-positives, and a value with high specificity but low sensitivity will result in false-negatives. Plotting the true-positive rate (sensitivity) against the false-positive rate (1-specificity) for a range of cut-offs gives a **ROC curve** (Fig. 14). The area under the ROC curve **(AUROC)**

describes the overall accuracy of the predictor, from 0.5 (not at all predictive) to 1.0 (a perfect predictor).

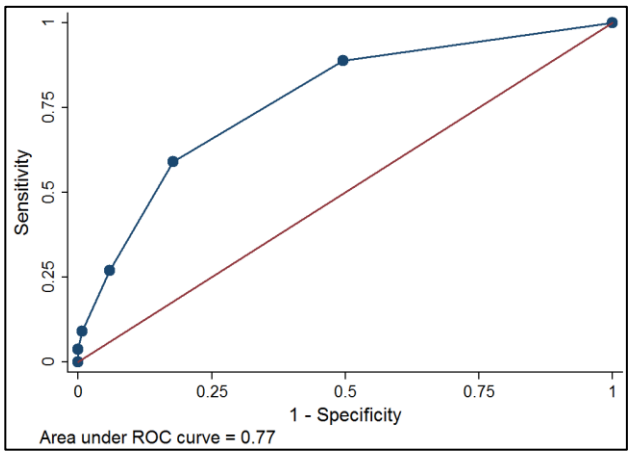

Fig. 14 Receiver operator characteristic curve for number of danger signs at admission to ICU and in-hospital mortality

Unpublished data from Study III

The **positive predictive value** is the probability of the outcome in a person who has the predictor and the **negative predictive value** is the probability of not having the outcome in a person who does not have the predictor. Unlike sensitivity and specificity, predictive values depend on the prevalence of the outcome and a predictor's performance differs greatly in settings of high or low prevalence.

Prediction models

As single predictors are rarely adequately accurate, predictors can be combined to provide multivariable **prediction models** (110,111). The model can estimate a probability than an outcome will occur. In critical care, the Acute Physiology And Chronic Health Evaluation (APACHE) and Simplified Acute Physiology Score (SAPS) are multivariable prediction models used to predict hospital mortality (112).

Prediction modelling was not chosen for the studies in this thesis due to five limitations. Firstly their performance is context-sensitive – an accurate model in one setting may have poor calibration or discrimination in another (111), meaning that the models developed in high-income settings may not be clinically useful in low resource settings. Secondly, existing models may include parameters that are not available in some settings – for example APACHE and SAPS require laboratory testing that are not routinely available in low resource settings. Thirdly, they require large sample sizes and several consecutive studies for development and validation, which precluded their development in this thesis (110).

The fourth limitation is that the prediction model may not provide accurate enough prediction for clinical use in individual patients, as in one study in Malawi (60). APACHE and SAPS that are used to evaluate the quality of ICU care are not recommended for individual patients (112). Indeed, there is a danger if predictive models are used inappropriately for individuals. For example, a reasonably accurate model with positive and negative predictive values of 0.8 would result in a false prediction in 20% of the patients. If the intended use of the model is for deciding whether to start a life-saving but hazardous treatment, admit a patient to a

hospital or an ICU, or to inform the patient about an upsetting diagnosis, then the exclusive use of such a model could be harmful. This limitation applies to all predictors including the single parameter danger signs in **Studies III** and **IV** – prediction in medicine is notoriously difficult. The information from prediction models should be supplemented with other diagnostic tests and clinicians' judgement to avoid false predictions for individuals.

The final limitation is of great importance in low resource settings. Determining the score in a multivariable prediction model for an individual patient may be too complicated or time-consuming for over-stretched health workers. Even a few minutes to add up scores can be impossible when resources are scarce.

One further consideration influenced the decision to use single parameters instead of prediction modelling in **Study III**. Using single parameters allows for the specific treatment directives developed subsequently in **Study IV**. For example, a hypotension danger sign can be linked to the treatment directive of intravenous fluid administration, as in the VSDT protocol. The compound scores used in prediction modelling do not have this useful attribute.

IMPLEMENTATION SCIENCE

The third and fourth aims of the thesis were to evaluate if VSDT improves the *acute treatment* and *outcomes* of patients with deranged vital signs (**Study IV**). These aims necessitated an intervention. An **intervention** is a change to practice, for example, the use of a new drug or a new working routine. The VSDT protocol is an intervention. **Implementation** is the execution of a plan for a change – i.e. the method by which the intervention is introduced (113).

There is increasing awareness of the importance of the choice of implementation methods for interventions aimed at improving the quality of care. **Implementation science** studies the best methods for promotion of evidence-based practices into routine care (114). Successful implementation methods are often compatible with existing practices, do not require substantial effort, are perceived as feasible, have early local involvement including local champions, include raising awareness and dissemination of new knowledge, involve ongoing troubleshooting, include improvements that are understood and desired and use methods that are compatible with organisational structures, leadership and regulations (115,116). Single implementation methods such as reminder techniques, educational materials, audit and feedback or educational outreach only improved performance by 6-14% in one meta-analysis (117). Multifaceted implementation methods sometimes show better results than single methods (118), although this has been questioned (119). A multi-faceted approach worked well in paediatric inpatient care in Kenya (120). The implementation method chosen in **Study IV** built on the above knowledge and was multi-faceted and context-appropriate, situated within an established Tanzanian-Swedish collaboration (MKAIC) and designed in close collaboration with doctors and nurses working on the ICU at Muhimbili.

In critical care, evidence for the best implementation methods is sparse. It has been argued that a proportion of the resources used for developing ICU guidelines or protocols must be dedicated to the implementation strategy (121). ICU protocols have produced some good results (14,122). A protocol for early monitoring and management of sepsis in Uganda led to a reduction in 30-day mortality by 12% (123). Another sepsis protocol in Zambia showed no mortality benefit. However, many of the patients had sub-acute tuberculosis or HIV infections which could explain these negative findings (124). Recommendations for sepsis care in resource limited settings have been published, but their use has not yet been studied (125). In order to be appropriate for the low resource context, the implementation of the VSDT protocol in **Study IV** utilised the concept of "task-shifting". Task-shifting (also called task-sharing) is one method of implementation that allocates aspects of health-service delivery to less costly and more available health workers – for example nurses can give care instead of physicians when access to physicians is limited (126). Task-shifting has been effective and safe in obstetrics (127), HIV-treatment (128) and surgical care (129) but has not previously been trialled in critical care.

The implementation in **Study IV** had mixed success. Evaluation of the implementation was conducted by assessing acute treatments when deranged vital signs were identified – i.e. adherence to the VSDT protocol. The results indicate that practices were changed – there were significant increases in acute treatments given for deranged vital signs both at admission and during the care on the ICU. A particular success was an increase in acute treatment of hypotension. However, the VSDT protocol stipulated that *all* deranged vital signs should receive an acute treatment, and yet the post-implementation adherence to protocol was only 16.6% (35% for hypotension). This low adherence could be seen as a low "dose" of the intervention, suggesting that the implementation method had some deficiencies. The reasons are not fully understood and will be the focus of further research. Possible explanations include a lack of full buy-in by influential individuals, a failure of the information and training to establish a deep understanding among staff or more generally a low organisational capacity for change. The implementation was designed to be low-cost and pragmatic, embedded within the existing hospital structure. Most of the researchers were based in Sweden and spent limited time in Tanzania in order to reduce expenditure and avoid introducing the confounder of external expertise. This challenging model of implementation from a distance could explain the low adherence. Despite these issues, improvements were seen, and interesting questions were raised about whether a greater adherence to protocol could improve outcomes beyond the observed mortality reduction for hypotensive patients.

INTERPRETATION OF FINDINGS

This thesis has three main findings. In low resource settings:

1. There is a lack of good quality critical care
2. Deranged vital signs identify critical illness
3. Critical care can be simple and appropriate

There is a lack of good quality critical care in low resource settings

In Study II hospitals in Tanzania were found to lack many structures for critical care. The weakest aspects were human resources and training, routines for managing the critically ill and infrastructure. Similar problems could be seen in **Studies III** and **IV**, where a university hospital had very few ICU beds, a lack of trained staff, and a lack of routines for identifying and treating patients with deranged vital signs. In **Study IV**, only 2.9% of deranged vital signs received an acute treatment on the ICU prior to the introduction of a Vital Signs Directed Therapy protocol. The in-hospital mortality rates of 50% seen in **Studies III** and **IV**, may suggest underlying quality issues.

Data from only a few centres have been used in this thesis. **Study II** was from ten hospitals and **Studies III** and **IV** were from one university hospital, all selected using convenience sampling. Generalising to other hospitals in Tanzania must be done with caution. However, similar results were found in the only other research on critical care from Tanzania, a recent retrospective study of four ICUs (130). The investigators found deficiencies in infrastructure, personnel and resources and an ICU mortality rate of 41%. An encouraging finding from **Study II** was the good availability of drugs and equipment. This suggests that improvements to critical care should target the infrastructure, routines and training of health workers.

Supporting evidence comes from related medical disciplines in Tanzania. In obstetric care, improving training, routines and protocols have been identified as key to reducing maternal mortality (94,131). In a survey of emergency and surgery services in 48 health facilities, human resources and infrastructure as well as medical equipment were lacking (93). In a nationwide survey in 2006 only 19% of hospitals had the facilities to support 24-hour emergency services (132). Interestingly, in the nationwide survey, the Ministry of Health's plan for reducing maternal and child deaths (133), and in an external health system evaluation by USAID in 2011 (92) there were no indicators for, or even discussion of, critical care or intensive care.

While this thesis contains results from only one LIC, reports from other countries are consistent with its findings. In a survey of African anaesthetists, only 1.5% reported that their hospital had the required facilities, equipment and drugs to implement international guidelines for the care of patients with sepsis (41). These results were mirrored in more thorough surveys from Congo and Mongolia, where none of the hospitals surveyed had the necessary resources for implementing the guidelines (134,135). In the Solomon islands,

critical care lacked infrastructure, trained staff and support services, as well as drugs and equipment (136). In paediatric inpatient care, similar problems with training, routines, monitoring and treatments of sick children have been seen (137,138). Several authors have discussed the lack of good quality critical care in LICs, although they acknowledge that the evidence base is weak (34-36,50,51,139).

Poor quality care in low resource settings has also been seen in the related medical disciplines of emergency care, surgical care and anaesthesia. Emergency care is often lacking in hospitals and there are increasing calls for worldwide improvements (140-143). Five billion people do not have access to safe, affordable surgical and anaesthesia care when needed (2,76). Problems were identified in the quality of anaesthetic care in Uganda (144), Zambia (145) and Tanzania (146). The underlying determinants of the quality of critical care are poorly understood but are likely to be the same as for these other time-dependent specialties.

The in-hospital mortality rate of 50% and ICU-mortality rate of 44% for all admissions over 16 years of age (65% and 58% respectively for unplanned admissions) in **Study III** is strikingly high, especially given the young age of the patients. These figures are consistent with those in the survey of four ICUs in Tanzania including Muhimbili (130) and are higher than the average in-hospital mortality of 22.4% reported in a global ICU survey in 2014 (147). The findings could indicate a poor quality of care or a very sick patient selection. As many patients had severe physiological derangements at admission and 9% died within 12 hours, it is likely that the effect of the latter was substantial and a large proportion of patients were not salvageable. However, the lack of routines, human resources, training and treatment of deranged vital signs as found in **Studies II** and **IV** suggest that there is substantial scope for improving quality.

Deranged vital signs identify critical illness in low resource settings

In **Study I**, hypotension, tachycardia and decreased level of consciousness at admission to hospital were associated with mortality. The risk of dying increased as a compound EWS increased. In **Study III**, a severe derangement in any vital sign at admission to ICU was associated with mortality and mortality increased with the number of deranged vital signs.

Deranged vital signs have been seen to correlate with poor outcomes in many studies in high-income countries (53-55,59,148). They form the basis of the Early Warning Scores and Rapid Response Teams that have shown impressive reductions in hospital mortality rates (16,18,19,67,149,150).

This thesis adds results from Tanzania to the sparse data on the use of vital signs in critical care in low and middle income countries. The South Africa Triage Scale has been developed which is showing promising results but has not been rolled out nationwide (151). In India, systolic blood pressure, heart rate, and Glasgow coma scale were associated with mortality in adult trauma patients (152). In Malawi, low oxygen saturation, low temperature, high

respiratory rate and reduced conscious level were associated with mortality (60). In two studies of septic patients in Uganda, deranged vital signs were associated with in-hospital mortality (42,153). The findings in this thesis from a university hospital and two smaller hospitals support the plausible supposition that deranged vital signs have a similar ability to identify critical illness when resources are limited as in high resource settings. It should be stressed, however, that the associations with mortality should not be interpreted as predictions for individual patients. The presence of danger signs does not predict that the patient will die, and the absence of danger signs does not predict survival. As biology and pathologies are so heterogeneous, it is unlikely that predictive models based on simple vital signs will ever have sufficient predictive value, and the information provided by vital signs should be seen as part of the overall clinical picture.

There are signals that hypotension may be the vital sign with the strongest association with death and the most amenable to intervention. For hypotension, the odds ratios of death were between 2.1 and 6.3 in **Study I** and 16.2 in **Study III**. In a recent study of trauma patients in India, hypotension was also found to be one of the two best predictors of early mortality (the other was Glasgow coma scale) (152). In the Malawian study, hypotension was not associated with mortality, but that may be because a high cut-off of <100mmHg was used (60). In **Study IV** the greatest improvement in acute treatments following implementation of the VSDT protocol were seen in hypotensive patients. This could be explained by a low baseline level of acute treatment for hypotension, a relatively high baseline level of treatment for other deranged vital signs, the simplicity of the acute treatment of IV fluids for hypotension, or less successful implementation of the actions for the other danger signs. Moreover, in contrast to the whole cohort, mortality rates in hypotensive patients were reduced from 92.3% to 69.2% giving a numbers-need-to-treat of 4.3. Treating hypotension with fluid boluses is standard practise in critical care (154-156), however there is some recent evidence calling for caution when administering fluid boluses to African children with febrile illness (157) or to adults with sub-acute sepsis (124).

Critical care can be simple and appropriate for low resource settings

Studies I and **III** found that single deranged physiological parameters were as well associated with mortality as more complex EWS compound scoring systems. In **Study IV** a context-appropriate multi-faceted methodology succeeded in implementing a VSDT protocol onto an ICU. The simple VSDT protocol, used by local staff, led to improvements in the care given for deranged vital signs and improved outcomes for some of the patients.

There were however some limitations with the methodology in **Study IV**. It was a single centre study, conducted in a university hospital and so transferring the results to other settings must be done with caution. It also had a before-and-after design leading to a potential risk of temporal confounding (the effects of other changes on the ICU during the study that were not related to the research project). It could be seen, however, that the

increase in acute treatments occurred at the same time as the implementation, strengthening the evidence of a causal relationship. Moreover, interviews with the head nurse on ICU did not reveal any major changes to the ICU during the study period.

Although it can be concluded that the implementation led to changes in patient care, the exact nature of the intervention deserves some comment. The main aspect of the intervention was the use of the VSDT protocol. Pre-implementation, the protocol was not used and afterwards the increased treatment of deranged vital signs suggests that it had become part of the care on the unit. However, some effects could have been caused by the multi-faceted implementation itself, or by the ongoing research activities. The training may have led to new knowledge about vital signs or other aspects of critical care. The increased interest and international nature of the research may have raised morale on the unit. Ongoing data collection may have changed staff behaviour. In other words, the change in care, which is synonymous with the *intervention*, can itself be complex and not solely be the use of the VSDT protocol. If the research would have been purely interested in the protocol, then these aspects should be regarded as "introduced confounders". However, elements of such effects were expected and unavoidable, and as the research was pragmatic and was interested in the effect of the whole "bundle" of implementation and changed practices, then it was reasonable to see them as a part of the research study. The observed effects may be more context-specific than the protocol itself which may limit transferability of the results to other settings.

The relative merits of single and compound scoring systems are debated. Single parameter danger signs have been used in the Karolinska University Hospital's Medical Emergency Team protocol (148) which reduced in-hospital mortality by 10% (19). While compound scores have shown good results in some settings (57,67,68,158), some compound scoring systems also allow extreme single parameter values to trigger escalation of care (159). A simpler index has been developed in Uganda, but still involves inefficient calculations and dubious added benefit (153). This thesis did not have the aim to find the best-fitting multi-parameter prediction model, but focused instead on single parameter danger signs. Danger signs do not require a calculation of a score and so are simpler and less resource intensive, making them more appropriate in low resource settings. They have the added positive attribute of allowing a direct link to a clinically relevant action, ensuring that the identification of critical illness can be followed by acute treatments, as in **Study IV**.

There are several reports of simple and low-cost improvements to the care of critically ill patients. Emergency triage and treatment for children in a hospital in Malawi cost only US$1.75 per patient and reduced hospital mortality by 50% (160). Oxygen therapy can cost less than 1 cent per litre (161) and when oxygen was introduced in Papua New Guinea, child mortality was reduced by 35% at a cost of US$50 per disability-adjusted life-year averted (162). In Uganda, a simple and inexpensive sepsis protocol reduced mortality by 26% (123) and emergency surgery was found to be more cost-effective than other public health interventions (80).

It is salient that simple critical care is not only appropriate for low resource settings. Initiatives such as the use of vital signs, rapid response systems, checklists and protocols are being promoted even in high-income settings, with remarkable improvements in outcomes (13,14,18,61,63). Good quality, simple and appropriate critical care is a global necessity and is feasible, even in low resource settings (see box).

Box: What good quality critical care in a low resource setting could look like

A **trained**, experienced nurse using a locally approved **triage system** based on deranged **vital signs** quickly identifies critically ill patients in the **Emergency Department**. The nurse calls for **assistance** from senior colleagues. They take the patients to the **resuscitation room** where acute treatments are given from the well-stocked **emergency box**.

Once stabilised, the patients are transferred to an **ICU**. On the ICU, there is a higher nurse to patient ratio than on the general wards and all the staff are **trained** in critical care. The patients are **monitored** closely and a Vital Signs Directed Therapy **protocol** assists the identification of **danger signs** and stipulates the treatments to give.

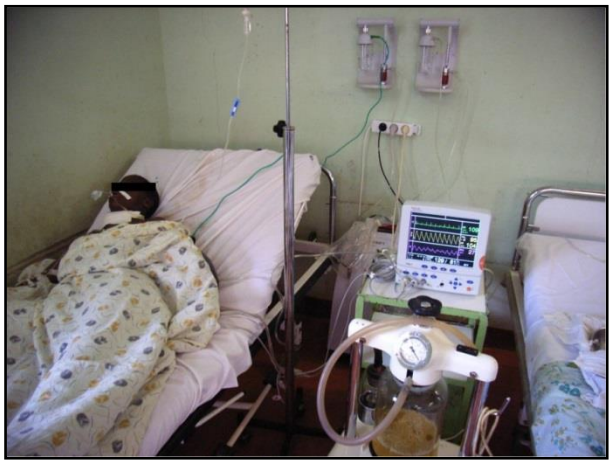

Fig. 15 Critical care in a low resource setting

Photo: Tim Baker

Observation and treatment charts ensure clear record keeping and early detection of deterioration. Clinicians **review** the patients regularly, management is **adjusted** if their condition changes and there are open **communication** channels between nurses and clinicians 24 hours/day. **Emergency drugs and equipment** are kept on the ICU, checked regularly and restocked whenever something is used. Staff and relatives do not need to leave the ICU to fetch or pay for emergency supplies.

User-friendly **guidelines** for managing common medical emergencies are visible in the ICU. Unconscious patients are nursed in the **lateral position** and turned regularly to prevent pressure sores. **Suction** is available to keep airways clear. **Hypoglycaemia** is suspected early and treated liberally. Patients are monitored with a **pulse oximeter** and **oxygen** is available in concentrators and cylinders. Dehydration and shock are prevented and treated with oral rehydration solution and intravenous **fluids**. **Pain relief**, nutrition and supportive therapies are given according to established local **routines**.

When the patients have recovered, they are transferred to a general ward. On the ward, nurses practicing **ward-based triage** using **vital signs** observe their recovery and can refer back to ICU if their condition worsens. The hospital's **critical care service** is feasible and saves lives.

CONCLUSIONS

- There is a lack of good quality critical care in low resource settings. The main barriers are routines, human resources and infrastructure. Patients with deranged vital signs are rarely given acute treatments on ICU and mortality rates are high.

- Deranged vital signs are associated with mortality in low resource settings and single deranged physiological parameters are as useful as compound scoring systems for identifying critical illness.

- The Vital Signs Directed Therapy protocol improves the acute treatment of patients with deranged vital signs.

- Vital Signs Directed Therapy improves outcomes for some critically ill patients

RECOMMENDATIONS

In this thesis I have described the lack of good quality critical care in low resource settings and shown that critical care based on vital signs can be simple and appropriate.

Critical care is neglected and should be brought up the policy agenda. Health ministries need to understand its importance in reducing mortality and achieving health goals and include critical care in health system planning. Care for the sickest patients should be prioritised in health facilities. International and national standards should be developed. Critical care guidelines for hospitals should be written, human resources increased and training both pre-service and in-service improved. Supervision and peer-support of critical care services would be valuable, using critical care health workers to evaluate health facilities against the accepted standards.

International organisations can take an active role. Links with hospitals and universities, such as the MKAIC collaboration, can provide dynamic environments for the sharing of experiences, knowledge acquisition, support and motivation. Professional bodies such as critical care or anaesthesia societies and non-governmental organisations such as Life Support Foundation can support the sustainable development of critical care. Improvements to critical care should be an integrated part of overall health system strengthening.

Critical care should maintain a focus on simple, appropriate treatments. There is a danger that critical care is interpreted as requiring expensive high-tech interventions such as dialysis and mechanical ventilation. While life-saving for some individuals, they risk a diversion of resources and energies from other care. Remember Voltaire's 250 year old cautionary insight: "*the best is the enemy of the good*".

Critical care in low resource settings should be evidence based. Future research should answer:

1. Why has critical care been under-prioritised in low resource settings? (Policy analysis)
2. How can the quality of critical care be evaluated? (Development and validation of quality standards and indicators)
3. Is the quality of critical care similar in other low resource settings?
4. What are the bottlenecks to improved quality in critical care and how do these differ between low resource settings?
5. What is needed to overcome these bottlenecks at the policy level, the health system level and at the health facility level?
6. Does the VSDT protocol reduce mortality in other low resource settings?
7. What facilitates or hinders the implementation of the VSDT protocol or other critical care improvements?
8. What is the burden of critical illness in health facilities in low resource settings and globally?
9. What are the effects and the cost-effectiveness of critical care interventions such as medical emergency teams, triage, ICUs, critical care training, increased vital sign monitoring and the VSDT protocol?

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A B C, its easy as 1 2 3
Jackson 5

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APPENDIX

Structure Standards for Emergency and Critical Care in Low Income Countries

The hospital should have

An infrastructure designed for managing emergency and critically ill adults and children

Infrastructure Indicators	1 2	Designated Triage Area For adults For children
	3 4	Designated Emergency Room / Area For adults For children
	5 6	An ICU or a designated area of a ward for critically ill patients For adults For children

Sufficient human resources for managing emergency and critically ill adults and children

Human Resource Indicators	7	Nurse/other health worker either working in the ER or having the task of immediately going to the ER if a critically ill patient arrives
	8	A clinician either working in the ER or being "on-call" for the ER if a critically ill patient arrives
	9	A designated "Medical Head of ICU"
	10	A higher ratio of staff: patients on ICU than on general wards

Sufficiently trained staff for managing emergency and critically ill adults and children

Training Indicators	11	Nurses and clinicians involved in adult triage have been trained in adult traige
	12	Nurses and clinicians involved in emergency care of adults have undergone training in emergency care
	13	Nurses and clinicians involved in critical care for adults have undergone training in critical care
	14	Nurses and clinicians involved in paediatric triage have been trained in paediatric triage
	15	Nurses and clinicians involved in emergency care of children have undergone training in emergency care
	16	Nurses and clinicians involved in critical care for children have undergone training in paediatric critical care

Essential drugs for emergency and critical care

Drug Indicators	17	Oral Rehydration Solution
	18	IV glucose
	19	IV crystalloid (Normal Saline ± Ringers Lactate)
	20	Diazepam
	21	Paracetamol
	22	Parenteral Penicillin (or equivalent)
	23	Parenteral Gentamycin (or equivalent)
	24	Parenteral Quinine (or other anti-malarial)
	25	Ketamine
	26	Lidocaine
	27	Adrenaline
	28	Atropine
	29	Frusemide
	30	Nifedipine or other anti-hypertensive
	31	Aminophylline
	32	Salbutamol (for inhaler or nebuliser)
	33	Hydrocortisone
	34	Insulin
	35	IV/IM opioids
	36	Naloxone
	37	Thiopentone
	38	Succinylcholine

	39	Non-depolarising muscle relaxant
	40	Oxytocin/Ergotamine
	41	Magnesium Sulphate
	42	Phenobarbital / Phenytoin
Essential equipment for emergency and critical care		
Equipment Indicators	43	Clock with second hand
	44	Gloves - clean
	45	Gloves - sterile
	46	Sharps disposal
	47	Running water & soap
	48	Oral airway (Guedel) – adult & paediatric sizes
	49	Suction machine (foot powered or electric) & tubing
	50	Laryngoscope (working)
	51	Endotracheal Tubes – adult & paediatric sizes
	52	Rigid neck collar or Sandbags/ towel rolls and head restraints
	53	Chest tube & underwater seal (or equivalent)
	54	Pulse oximeter
	55	Bag valve mask (Ambu bag)
	56	Stethoscope
	57	Foetal stethoscope
	58	Blood pressure cuff
	59	IV cannulae – adult size (eg 18G)
	60	IV cannulae – paediatric size (eg 22G, 24G)
	61	IV giving sets
	62	Needles
	63	Syringes – 2ml & 5ml
	64	Urine catheters & bags
	65	Gauze & bandages
	66	Skin disinfectant
	67	Torch
	68	Electricity 24hours/day
	69	Light suitable for clinical examination
	70	Bedside blood sugar testing device & strips
	71	Weighing scales
	72	Thermometer
	73	Refrigerator
	74	Nasogastric Tubes
	75	Oxygen concentrator / cylinder with face masks or nasal prongs and tubing
	76	System for ensuring continuous availability of oxygen (eg reserve electricity generator / reserve cylinders with good transport and refilling system)
Routines for managing emergency and critically ill adults and children		
Routines Indicators	77 78	System for categorising patients according to clinical urgency (triage) For adults For children
	79 80	System for prioritising the treatment of critically ill patients before stable patients For adults For children

	81 82	Admission registration and payment delayed until after triage and emergency treatment For adults For children
	83	ICU admission/discharge criteria
	84 85	Nurses have a routine of frequent observations of the patients (hourly or specified depending on clinical need) For adults For children
	86 87	Clinicians check patients (ward rounds) at least twice a day For adults For children
	88	There is a system for identifying critically ill patients on general wards and transferring to ICU (A "track and trigger" system)
Guidelines for managing emergency and critically ill adults and children		
Guidelines Indicators	89 90	Guidelines for triage For adults For children
	91 92	Guidelines for Emergency Care For adults For children
	93 94	Guidelines for Critical Care For adults For children
	95	Guidelines for Oxygen use
Support Services for managing emergency and critically ill adults and children		
Support Services Indicators	96	Lab with facilities and trained personnel to measure Haemoglobin
	97	Lab with facilities and trained personnel to measure blood glucose
	98	Lab with facilities and personnel to measure Serum Urea/Creatinine, Sodium and Potassium
	99	X-ray facilities and trained personnel for chest radiographs
	100	System for emergency blood transfusion
	101	System for making cross matched blood available within 1 hour of blood sample arriving in lab
	102	System for testing donor blood for the viruses HIV, Hepatitis B & C
	103	Lab with facilities and trained personnel to do direct microscopy & bacterial gram stain
	104	Lab with facilities and trained personnel to do bacterial culture and antibiotic sensitivities

IV intravenous; IM intramuscular;

Advanced Emergency & Critical Care Indicators

The hospital has:

1	Ventilator
2	Piperacillin/Meropenem
3	Colloid
4	Fresh Frozen Plasma
5	Propofol or Midazolam
6	Noradrenaline or Dobutamine
7	Invasive Blood Pressure Monitoring
8	Central Venous Pressure Monitoring
9	Aterial Blood Gas analysis
10	Syringe pump