Positive pressure ventilation at birth and potential pathways to newborn deaths in rural Tanzania

by

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Abbreviations

BA	Birth Asphyxia
CPAP	Continuous Positive Airway Pressure
ECG	Electrocardiogram
ENAP	Every Newborn Action Plan
FHR	Foetal Heart Rate
FRC	Functional Residual Capacity
GA	Gestational Age
HBB	Helping Babies Breathe
HIE	Hypoxic Ischemic Encephalopathy
HLH	Haydom Lutheran Hospital
HR	Heart Rate
MSAF	Meconium Stained Amniotic Fluid
NRM	Newborn Resuscitation Monitor
PEEP	Positive Expiratory End Pressure
PPV	Positive Pressure Ventilation
SDG	Sustainable Development Goals

WHO	World Health Organization

Definition of terms

Neonatal period: period from birth to 28 days of life

Neonatal mortality: Death of newborns per 1000 live births within 28 days of life

Early neonatal mortality: Death of newborn per 1000 live births within first 7 days

Intrapartum period: period from the onset of labour to the end of the third stage of labour (delivery of placenta)

Prematurity: newborn born before 37 completed weeks of gestation

Intrapartum-related neonatal deaths: deaths due to complications arising during the intrapartum period.

Summary

Background: There are 2.6 million neonatal deaths that occur globally each year, with more than 80% of these deaths occurring in low-income countries. In Tanzania, available estimates report that approximately 40,000 newborn deaths occur each year, mainly due to intrapartum-related causes, prematurity-related complications, and sepsis. The majority of intrapartum-related neonatal deaths can be avoided by improving care around births. Interventions that have the potential to reduce intrapartum-related neonatal deaths include foetal monitoring during labour, availability of emergency obstetric care, and newborn resuscitation at birth for non-breathing newborns. Low-income countries are faced with many challenges in providing this care, including unskilled providers and inadequate training strategies that do not support the acquirement and retention of skills in newborn resuscitation.

Aims: The overall aim of this thesis was to investigate the causes of early newborn deaths and the contribution of intrapartum-related events and their association with ventilation immediately after birth. Furthermore, we wanted to describe the human factors and interactions that influence effective newborn resuscitation practices in this rural setting.

Methods: We applied a mixed-methods design and conducted three studies from October 2014 to July 2017. An observational study of all admitted newborns, delivered at Haydom Lutheran Hospital (*n*=671) between October 2014 and July 2017, was conducted to determine the

presumed causes of 7-day newborn deaths and potential pathways contributing to death in this setting (Study I). A study that included the admitted newborns who received positive pressure ventilation in the delivery room (*n*=232) between October 2014 and November 2016 was then performed to compare ventilation characteristics with the newborn outcome at 7 days (Study II). Infants who died within the first 30 minutes of birth were excluded from both Studies I and II because they died in the delivery room. Building on the findings of the quantitative studies, a third study was conducted, consisting of in-depth interviews with midwives who performed deliveries and newborn resuscitations at Haydom Lutheran Hospital to explore factors affecting the provision of effective ventilation during newborn resuscitation (Study III).

Results: In Study I, intrapartum-related complications (birth asphyxia and meconium aspiration syndrome) contributed to almost two-thirds of all deaths within 7 days. Prematurity, presumed sepsis, and congenital abnormalities were other causes of death. Intrapartum hypoxia and prematurity were the major pathways leading to death. Severe hypoxia and hypothermia upon admission were important additional contributing factors.

In Study II, we showed that depressed newborns at birth who eventually died within 7 days had an abnormal foetal heart rate during labour, presented signs of bradycardia immediately after birth, and had delayed heart rate responses to positive pressure ventilation. Abnormal foetal heart rate during labour, heart rate at the end of positive pressure

ventilation, and duration of positive pressure ventilation were the perinatal predictors of death in this setting. These newborns developed seizures and moderate/severe encephalopathy, likely related to intrapartum hypoxia. Despite inconsistencies in adhering to the Helping Babies Breathe algorithm, the tidal volume and heart rate responses that were recorded did not significantly influence the outcome of death or survival.

In Study III, midwives reported the importance of monitoring labour and being prepared for resuscitation before delivery. They also cited good teamwork and frequent ventilation training as factors to facilitate effective ventilation. Barriers to effective ventilation were identified as being anxious and/or feeling fear during ventilation, and difficulties in assessing clinical responses during ventilation.

Conclusion: The findings in this PhD thesis demonstrate the contribution of intrapartum-related neonatal deaths to early newborn mortality in a rural sub-Saharan setting. Furthermore, the data demonstrate a link between intrapartum events, likely through interrupted placental blood flow, and a state of depression in the foetus at birth, as represented by low heart rate at birth, delayed heart rate responses to positive pressure ventilation, and, eventually, death. Hypothermia and hypoxia during admission likely played a role in increasing mortality. The included studies highlight the potential for improving intrapartum care through enhanced foetal monitoring during labour to identify those at risk, as well as the benefits of optimizing

positive pressure ventilation during resuscitation in the delivery room. The latter should be the focus of frequent resuscitation training sessions to address the providers' uncertainties and inconsistencies during resuscitation. Frequent resuscitation training should build the confidence of providers to quickly assess newborns immediately after birth, and to act without delay in order to optimize the provision of positive pressure ventilation.

Publications included

This thesis is based on the following papers which will be referred to in the text by their Roman numerals:

Study I

Moshiro R, Perlman JM, Mdoe P, Kidanto H, Kvaløy JT, Ersdal HL.

Potential Causes of Early Death Among Admitted Newborns in a Rural Tanzanian Hospital. *PLoS ONE*. 2019;**14**(10):e0222935

Study II

Moshiro R, Perlman JM, Kidanto H, Kvaløy JT, Mdoe P, Ersdal HL.

Predictors of death including quality of positive pressure ventilation during newborn resuscitation and the relationship to outcome at seven days in a rural Tanzanian hospital. *PLoS ONE*. 2018;**13**(8):e0202641.

Study III

Moshiro R, Ersdal HL, Mdoe P, Kidanto H, Mbekenga C.

Factors affecting effective ventilation during newborn resuscitation: a qualitative study among midwives in rural Tanzania. *Global Health Action*. 2018;**11**(1):1423862

Contents

1 Introduction

The burden of neonatal mortality is a global concern, with 2.5 million newborns lives lost every year (1). Global communities, facilitated by various international agencies, have been working together to identify various strategies in order to accelerate the reduction of newborn mortality. In Tanzania, approximately 40,000 neonates die each year within the first 28 days after birth (2). The risk of death is significantly higher during the first 7 days, when approximately two-thirds of all neonatal deaths occur. This burden of neonatal mortality is accompanied by a significant burden of maternal mortality and stillbirths (3). The government of Tanzania has responded with several strategies to improve the outcomes of pregnancies and has stated that the reduction of maternal, neonatal and child deaths is a high-ranking priority.

1.1 Sustainable Development Goals

In August 2015, United Nations (UN) member states agreed on a set of actions and goals for the next 15 years; the 2030 Agenda for Sustainable Development, or the Sustainable Development Goals (SDG). These are a set of 17 goals and 169 targets that seek to improve the lives of people and protect the planet, while ensuring prosperity and peace for the next 15 years (4). The SDGs seek to build and expand upon the Millennium Development Goals (MDGs) (5), which were implemented in 1990 and extended through to 2015, and which aimed to deliver sustainable economic, social, and environmental development worldwide.

During the implementation of MDG number 4 (Child Health), the global under-5 mortality rate was reduced from 12.7 million (1990) to 6.0 million (53%) (2015). This absolute reduction was not matched by the decrease in neonatal mortality (from 5.1 million to 2.7 million (47%)). Consequently, the relative proportion of neonatal mortality to the under-5 mortality rate increased from 40% to 46% (1) (Figure 1). In Tanzania, this slow reduction in neonatal mortality was mainly a result of investments in programmes such as immunization, malaria prevention, and Integrated Management of Childhood Illness (IMCI) that targeted the older paediatric population during the initial 15 years of the MDGs' implementation (2), which did not have an effect on the newborn group. One of the key focuses of SDG goal number 3 is to reduce the number of deaths of children aged under 5 to 25 per 1000 births (from 67 per 1000 births in Tanzania) and reduce newborn mortality to 12 per 1000 live births (from 25 per 1000 births in Tanzania) by 2030 (4). With the current rate of reduction in newborn mortality, Tanzania will struggle to achieve this target unless efforts are made to accelerate progress and reduce newborn deaths from 40,000 to 24,000 by year 2030.

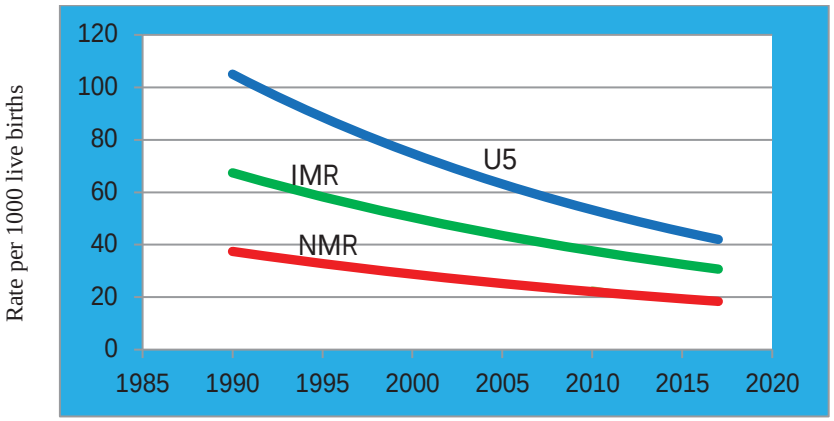

Figure 1: Global under-5 mortality trends from 1990 to 2018. U5M, under-five mortality; IMR, infant mortality rate; NMR, neonatal mortality rate. Source: UNICEF/WHO (2018)

1.2 Burden of neonatal mortality

The burden of neonatal mortality is significant in low-income countries compared to high-income countries. Sub-Saharan Africa and Southern Asia accounted for 80% of the 2.5 million neonatal deaths that occurred globally in 2017 (5,6). Despite an overall decline in the mortality rate of 41% for Sub-Saharan Africa, the number of neonatal deaths did not decline in 23 of these 46 countries from 2000 to 2017.

In Tanzania, under-5 mortality declined from 131/1000 in 2000 to 49/1000 in 2017, while neonatal mortality declined by less than half, from 38/1000 to 21/1000 in the same period (1,2). This reduction in neonatal mortality is not seen as a true decrease, as previous Tanzanian Demographic Health Surveys, as well as the estimates from the World Health Organization (WHO) Global Health Observatory data (6), have

overlapping confidence intervals, indicating a low precision and absence of true progress. Approximately 40,000 newborns die each year due to 3 major causes: intrapartum-related neonatal deaths, prematurity-related complications, and infections (2,3). Sub-national variation exists in neonatal mortality (7) due to variation in provisions and the use of health services in different regions in Tanzania, with rural areas at a disadvantage compared with urban areas (2,8).

1.3 Causes of neonatal mortality

Globally, 3 major causes are estimated to account for approximately 75% of all neonatal mortality: intrapartum-related neonatal deaths (23%), infections (15%), and prematurity-related complications (36%) (6,9) . Neonatal mortality can be further sub-divided based on time of death, into: immediate (24 hours), intermediate (7-days), and later (until 28 days). Nearly half of the neonatal deaths occur within the first 24 hours, and two-thirds by day 7 (10). Causes of early neonatal mortality differ slightly from those for mortality between 7 and 28 days. Intrapartum-related neonatal deaths and prematurity-related complications are the predominating causes of early neonatal mortality (11,12). In Tanzania, the causes of neonatal mortality are intrapartum-related neonatal deaths (30%), infection (30%), and complications of prematurity (25%) (2,3) (Figure 2). Previous reports in Tanzania have indicated a higher proportion of intrapartum-related neonatal deaths, i.e., 60% of 24-hour and 40% of 7-day neonatal mortality (13,14).

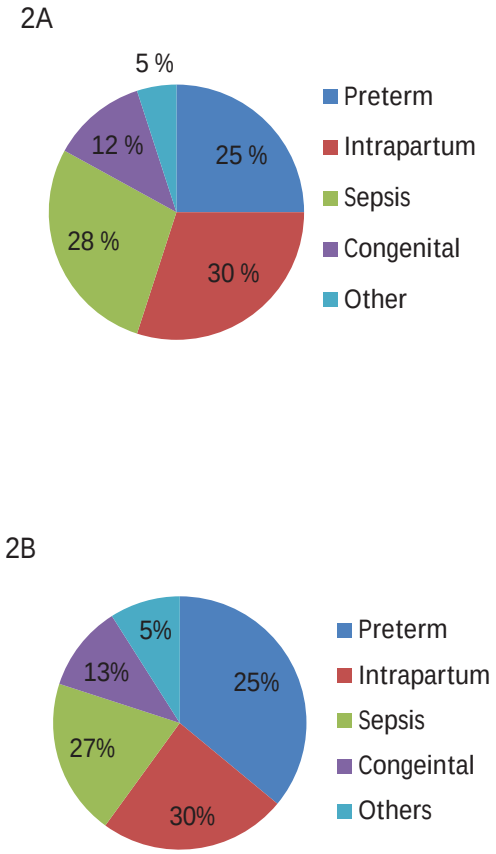

Figure 2: Causes of neonatal deaths. 2A - Global causes of neonatal deaths. 2B - Causes of neonatal deaths in Tanzania. Source: Afnan-Holmes et al. (2015), WHO (2018)

Intrapartum-related neonatal deaths, including birth asphyxia, account for more than one million deaths globally (6), where an additional one million suffer from morbidities such as brain damage (15). These deaths

are mainly a result of the interruption of placental blood flow, with subsequent ischemic injury to the brain.

The details of this process of interruption of placental blood flow will be discussed in later sections, however, the foetus may respond to a hypoxic state in-utero by passing meconium. Meconium is a thick, black-green mucoid chemical substance that is passed as stool after birth. The passage of meconium in-utero is considered a sign of foetal stress, and, thus, meconium stained amniotic fluid (MSAF) may be considered a risk factor for adverse perinatal outcomes (16). MSAF is noted in 10–20% of all deliveries (17,18), and complications associated with MSAF (e.g., meconium aspiration syndrome, pulmonary artery hypertension) may contribute to 4–10% of newborn mortalities (14).

While complications associated with MSAF in HICs have decreased substantially in recent years because of improved obstetric and neonatal practices, the situation still needs significant improvement in low- to middle-income countries. In one study conducted in a resource-limited setting, one-third of neonates with severe MAS were delivered post-term, and 50% of the mothers did not have electronic monitoring intrapartum, despite having MSAF (19). The identification of infants at risk of intrapartum hypoxia remains a major endpoint for preventing MSAF-associated complications.

Prematurity is the leading cause of death in children under 5 years of age (9). Prematurity accounts for 10% of all deliveries globally, and three-quarters of preterm births are found in South Asia and Sub-Saharan

Africa (20). The survival rate of premature newborns varies significantly around the world, with 90% of premature births prior to 28 weeks surviving in high-income countries compared to only 10% in low-income countries (20,21). Lung immaturity contributes to early death in premature newborns (22) and requires respiratory support immediately after birth, which may not be available in many low-income countries. Likewise, infection, another major cause of newborn mortality, contributes to between 10% and 30% of all newborn mortalities in Tanzania (2,3,14). Infection affects both term and preterm babies, with preterm babies being more susceptible due to their immature immune system. Clinically, infections in newborns present with non-specific signs and symptoms, necessitating laboratory parameters for confirmation. Ideally, all newborns suspected of sepsis should have a blood culture, complete blood count, and/or serial C-reactive protein tests done before commencing antibiotics. However, obtaining blood cultures consistently is still a challenge, due to the inconsistency of availability of stock and equipment. Therefore, the diagnosis of sepsis relies more on clinical signs and limited results, which may not be sufficient, resulting in the inappropriate use of antibiotics, subsequent antibiotic resistance, and a prolonged hospital stay. Recently, the WHO recommended several interventions that could improve premature survival, including continuous positive airway pressure (CPAP) for respiratory support and antibiotics for women in preterm labour (23). Implementing such recommendations requires careful planning,

including proper descriptions of facility-based burdens of disease to guide target-specific interventions.

Current estimates suggest that, every year, 6% of all newborns worldwide are born with a serious birth defect, 94% of which occur in low- and middle-income countries (24). The increased frequency of birth defects in low-income countries is fuelled by high birth rates, poverty, and limited access to sufficient nutrition in pregnant women, as well as limited access to pregnancy termination following prenatal screenings. Congenital anomalies contribute to up to 11% of all newborn deaths worldwide (6). In Tanzania, congenital anomalies are thought to contribute to around 10% of all neonatal mortalities; however, these estimates might not be correct due to an inability to confirm diagnoses, either clinically or by post-mortem.

1.4 Strategies to reduce/prevent early newborn mortality

Responding to the global burden of newborn mortality, the WHO and UNICEF launched the Every Newborn Action Plan (ENAP) in 2014, which set a goal of reducing preventable newborn deaths to less than 10 per 1000 live births by 2035 (25). This action plan is based on evidence that improving the quality of care around labour and delivery and during the first week of life, and care for small and sick newborns, will have the greatest impact on preventing newborn deaths.

1.4.1 Care around labour and delivery

One of the ENAP strategies includes investing more resources on the day of labour and birth, which includes providing optimum intrapartum care, such as FHR monitoring to identify those at risk, ensuring the availability of both basic and comprehensive emergency obstetric services, and increasing the number of competent healthcare workers in lower level facilities. The latter are essential to adequately monitor the foetus during labour and to help if the infant fails to establish spontaneous breathing after birth; both interventions are critical to the survival of newborns. The ENAP aims to achieve a skilled birth attendance rate of 95% by 2025. In Tanzania, the skilled birth attendance rate has increased; from 51% in 2010 to 64% in 2015 (3). Despite an increase in skilled birth attendance rate in several low-income countries, many countries are still behind in reaching a target of 90% with acceptable competency (26).

1.4.2 Essential newborn care

The WHO recommends a bundle of care referred to as Essential Newborn Care, which includes perinatal and newborn health practices delivered to every newborn, regardless of where it is born or its size, to ensure appropriate care at the most vulnerable period in a newborn's life (27). These practices include early initiation and exclusive breastfeeding, thermal care at birth, maximizing skin-to-skin contact, recognizing early signs of danger, and providing prompt treatment and referral. Other interventions include hygiene practices, such as cord-care and hand-washing. These interventions are simple and can be provided by a skilled

birth attendant or a trained community health worker. Essential newborn care is known to improve outcomes, but the challenge has been its coverage. A simple analysis, conducted by the Newborn and Child Health unit at the Ministry of Health in Tanzania, revealed that only 12% of healthcare facilities are implementing essential newborn care (28). The WHO recommends intervention coverage of at least 80% if the desired impact is to be attained.

1.4.3 Care of small/premature newborns

Newborns born before term have an increased risk of both morbidity and mortality, in part due to their immature organs. This predisposes the premature infant during delivery to events such as hypoxia, respiratory complications such as respiratory distress immediately after birth, temperature instability, and an increased risk of acquiring infection.

To ensure improved outcome of premature newborns, the management of preterm labour or of women at risk of preterm labour is important. The administration of antenatal corticosteroids to women at risk of preterm delivery has been associated with a reduction of preterm deaths and major morbidities, such as severe respiratory distress syndrome (29). Antenatal corticosteroids induce foetal lung maturation, leading to a reduced need for respiratory support that may not be available in low-income settings. Previous reports have indicated the need to be cautious when scaling up antenatal corticosteroid treatment in low-income settings. However, antenatal corticosteroids administered in hospital settings, in combination with maternal antibiotics when the woman is in

active preterm labour or experiences premature rupture of the membranes, will likely reduce mortality, as demonstrated by Massawe et al. (30). Maternal antibiotics are important, especially for preterm rupture of membranes associated with subclinical infection. Antibiotics will prevent ascending infection and subsequently reduce neonatal infection (31).

Among the interventions that have had a significant impact on small newborns is Kangaroo Mother Care (KMC). KMC is associated with decreased risk of neonatal mortality, and has been shown to protect against nosocomial infection and reduce risk of hypothermia (32). The protective effect of KMC is in part through the avoidance of hypothermia. Hypothermia has been linked to an increased risk of death in a dose-dependent manner (33). Hypothermia is still common in low-income countries, especially in infants who require admission. The WHO recommends skin-to-skin contact between the mother and the newborn immediately after delivery, and the contact should be maintained within the first hour. Newborns who need stabilisation are often separated and sent to a newborn care ward, increasing their risk of hypothermia (34).

The use of bubble CPAP in low-income countries is reported to be associated with a significant decrease in the mortality of premature newborns who present with respiratory distress syndrome (35). In high-income countries, intubation and administration of surfactant followed by placement on CPAP is part of standard care for infants presenting

with respiratory distress syndrome. Surfactant is still expensive for the majority of low-income countries, but less expensive CPAP devices are becoming available worldwide. Both bubble CPAP and the use of surfactant are more likely to be found in tertiary hospitals and private facilities in the majority of low-income countries. The implementation of interventions such as bubble CPAP on a large scale, together with competent personnel, is likely to improve the birth outcomes for premature newborns in such settings.

The management of infants at risk of infection is also a huge challenge in many low-income settings. Due to the limited ability to obtain blood culture results as mentioned above, the treatment of infections is mostly based on presumptive diagnosis and probable causative organisms are solely based on previous experience. All of the above interventions are likely to have a great impact when used in combination. A mother who receives a full course of antenatal corticosteroids and maternal antibiotics, and later delivers a preterm newborn who was stabilised, kept warm and started on CPAP immediately, has a much higher chance of leaving the hospital with her baby in her arms.

1.5 Intrapartum-related neonatal deaths

Complications during the intrapartum period, which may lead to intrapartum-related neonatal deaths, often occur as a consequence of interrupted placental blood flow. Such complications as prolonged labour, abruption placenta, or cord compression may commonly be referred to as intrapartum ‘events’ that may lead to intrapartum-related

neonatal deaths. Previously, newborns who were delivered following intrapartum-related events were classified as ‘birth asphyxia’, implying that the foetus had suffered oxygen deprivation. Asphyxia, by definition, is a state of impaired gas exchange leading to a progressive lack of oxygen to the tissues (36,37). The term ‘birth asphyxia’ originated from the Greek word ‘asphuxía’, which means ‘pulseless at birth’. Thus, infants who were born through intrapartum-related events were noted to have less movement and to be ‘without life’ at birth. However, the term ‘birth asphyxia’ is known to be imprecise, as it does not suggest the cause of the asphyxia (absence of respirations) itself. A newborn may fail to breathe at birth for multiple reasons, such as prematurity or congenital abnormalities of the lungs. A better term that has been suggested to represent death from intrapartum-related events is intrapartum-related neonatal deaths, as it states clearly where the likely cause of asphyxia has arisen from, i.e., during labour and delivery.

The diagnosis and confirmation of intrapartum-related neonatal deaths remains a challenge worldwide, but more so in low-income countries. Foetal intrapartum hypoxia has to be confirmed by the presence of biochemical changes that indicate impaired gaseous exchange as a result of the interruption of placental blood flow. Thus, an umbilical cord arterial pH of <7.00 is widely accepted as evidence of severe foetal acidaemia, which increases the risk of encephalopathy (38). In 1997, the WHO suggested a much more practical definition of birth asphyxia as ‘failure to initiate and sustain breathing after birth’. This definition is less

restrictive, as it may include newborns who fail to breathe due to other reasons, as discussed previously.

The foetus is affected by intrapartum events that interrupt placental blood flow. If the interruption is prolonged, it may result in the death of the foetus before birth (fresh stillbirths) or, if delivery takes place before death, intrapartum-related neonatal deaths may occur (39). The foetus will respond to prolonged interruption of placental blood flow and progressive hypoxia in several ways. These responses, such as decreased or absent foetal movements, changes in foetal heart rate (FHR) from the baseline rate (abnormal FHR), and/or meconium staining of the amniotic fluid, are sometimes used as proxies for diagnosing intrapartum hypoxia/foetal acidaemia. In the presence of the above signs, the foetus may be referred to as being in 'distress', indicating the possibility that the foetus is being subjected to an unfavourable hypoxia/hypoxemia environment (40). Intrapartum hypoxia can also be clinically suspected after birth, as infants tend to present with a blue/pale skin colour, low heart rate (HR), weak muscle tone, poor reflexes, weak/no cry, and difficulty breathing. These signs were initially observed by Virginia Apgar, who later developed a scoring system known as the Apgar score to assess the condition of newborns at birth (41) (Table 1). Since then, the Apgar score has been widely used as an additional marker of possible intrapartum hypoxia and acidosis, despite its widely reported limitations (42). The combination of a 5-minute Apgar score <7 and/or inability to initiate and/or sustain breathing after birth is widely used to identify intrapartum-related neonatal deaths in low-income settings.

Table 1: The Apgar score

Sign	Score 0	Score 1	Score 2
Heart rate	Absent	<100/min	>100/min
Muscle tone	Flaccid	Some flexion	Good
Reflexes	No response	Grimace	Good
Colour	Pale/blue	Blue extremities	Pink
Respirations	Absent	Weak	Good

Foetal distress, defined as progressive foetal hypoxia and/or acidaemia, secondary to inadequate foetal oxygenation, has been used as a proxy for increased risk of stillbirths and intrapartum-related neonatal deaths (40). Foetal distress is observed indirectly through the monitoring of FHR. The current consensus of the International Federation of Gynaecology and Obstetrics recommends a baseline normal FHR between 110 and 150 beats per minute (bpm) (43), despite the majority of other international guidelines recommending a baseline of between 110 and 160 bpm based on expert opinion (44,45). Any FHR persistently outside the specified range will be considered as abnormal (46). The aim of monitoring intrapartum FHR is to identify those foetuses at risk of intrapartum hypoxia so that delivery can be expedited. In high-income settings, continuous electronic FHR is the gold standard for identifying foetuses at risk of intrapartum hypoxia. On the other hand, the quality of intrapartum monitoring in low-income settings, including the correct

use/usefulness of partograms, has been shown to be sub-optimal (47). Improving the quality of care during the intrapartum period has therefore been linked with a reduction in both fresh stillbirths and intrapartum-related neonatal deaths in many low-income countries (48), as they share a common hypoxic ischemic pathway (39).

1.6 Newborn transition and resuscitation programmes

During delivery, a newborn has to undergo a transition from intra-uterine to extra-uterine life. The process of transitioning involves the onset of spontaneous breathing, where fluid-filled lungs are converted into air-filled lungs for gaseous exchange. It also involves transitioning from foetal circulation to newborn circulation.

1.6.1 Newborn transition

On average, a normal/healthy newborn starts to breathe approximately 5–10 seconds after birth (49,50). The initial and subsequent breaths help to clear the fluid-filled lungs and establish functional residual capacity (FRC), defined as air retained in the lungs at the end of each expiration (51). The establishment of FRC triggers several important physiological changes critical to the transition period. The expansion of the alveoli induces dilatation of the pulmonary blood vessels, followed by a decrease in pulmonary blood flow resistance, leading to an increase in

blood flow to the lungs (52). The removal of the low resistance placenta also increases a newborn's systemic vascular resistance. This is then followed by an increased cardiac output, increased HR, and improved oxygen delivery to the tissues.

Not all newborns will be able to undergo this transition smoothly. The most common reason for a newborn being unable to initiate spontaneous respiration is hypoxia and/or acidaemia, secondary to the interruption of placental blood flow, as described previously. Clinically estimating the duration of interruption is difficult. Dawes et al. (1968) suggested that newborns undergo stages during the interruption of placental blood flow. A brief interruption will induce primary apnoea, a state in which HR is above 60 bpm and blood pressure is compensated; newborns will invariably respond to stimulation and/or suction if delivered at this stage. If the interruption of placental blood flow is allowed to continue, bradycardia and hypotension will ensue, and the newborn is said to be in secondary apnoea and will require prolonged positive pressure ventilation (PPV) to establish FRC, reverse the hypoxic state, and correct the bradycardia (53) (Figure 3). When the interruption of placental blood flow is severe, the risk of hypo-perfusion to the brain is substantial. Such neonates present with apnoea and prolonged bradycardia, even following prolonged adequate ventilation and may need advanced care thereafter. Thus, an estimated 10% of newborns delivered who need basic resuscitation are thought to be in primary apnoea, and a further 3–6% who need more prolonged PPV are thought to be in secondary apnoea (50,54). A small proportion of newborns (less than 1%) will need

advanced care, such as intubation, medication and chest compressions followed by advanced neonatal care thereafter (55). Typically, these newborns will die in the delivery room in most low-income countries.

1.6.2 Newborn resuscitation

The estimated 3–6% of newborns requiring PPV is equivalent to 1 case in every 20 deliveries. Indeed, this is not a common occurrence, especially in facilities with a low number of deliveries. When a baby fails to breathe immediately after birth, a quick assessment must be performed while continuing with basic initial drying and stimulation. The International Liaison Committee on Resuscitation, a committee that reviews and makes recommendations on resuscitation guidelines every 5 years, recommends that providers spend the initial 30 seconds drying, stimulating, and keeping the baby warm, while at the same time, assessing for breathing and HR.

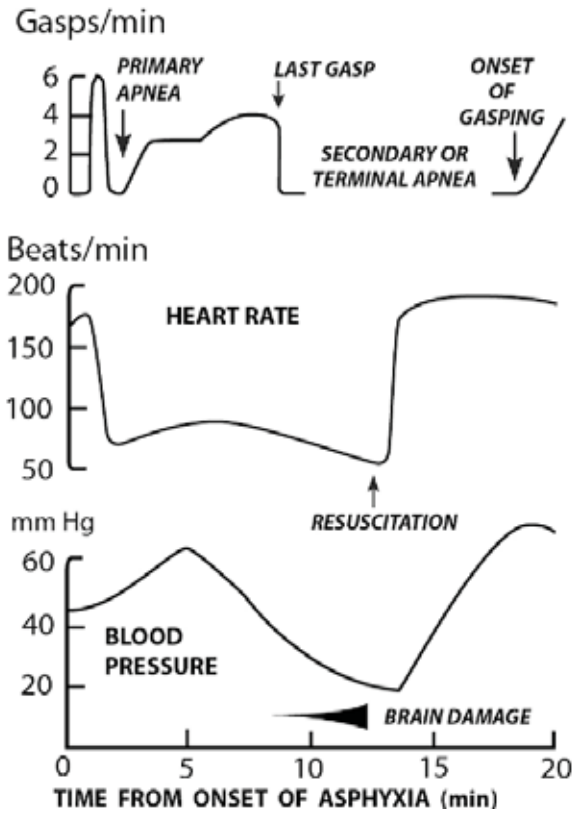

Figure 3: Dawes et al.'s (1968) monograph: Cardiologic and respiratory changes in near term rhesus monkeys asphyxiated by tying the umbilical cord and monitoring blood pressure, heart rate and breathing efforts.

According to the International Liaison Committee on Resuscitation, if the newborn has apnoea or is gasping for breath, and HR is <100 bpm, PPV should be initiated within 30 seconds (56). The subsequent steps and the direction of the action plan rely on assessment of HR responses as ventilation continues (Figure 4). This is due to HR being the most important clinical indicator of successful gaseous exchange, and hence is informative as to whether the resuscitation attempt is succeeding.

Furthermore, the International Liaison Committee on Resuscitation action plan involves the use of advanced algorithms, including medication, chest compressions, and endotracheal intubation.

The process of ventilation with a self-inflating bag and mask involves squeezing the bag while securing the mask properly around the mouth and nose of the newborn. The forceful entry of air into the lungs triggers the same physiological changes that lead to the establishment of FRC. In order for air to enter the lungs, the mask must be secured around the mouth and nose without leaks while the bag is being squeezed. The rise of the chest mostly confirms successful entry of air into the lungs.

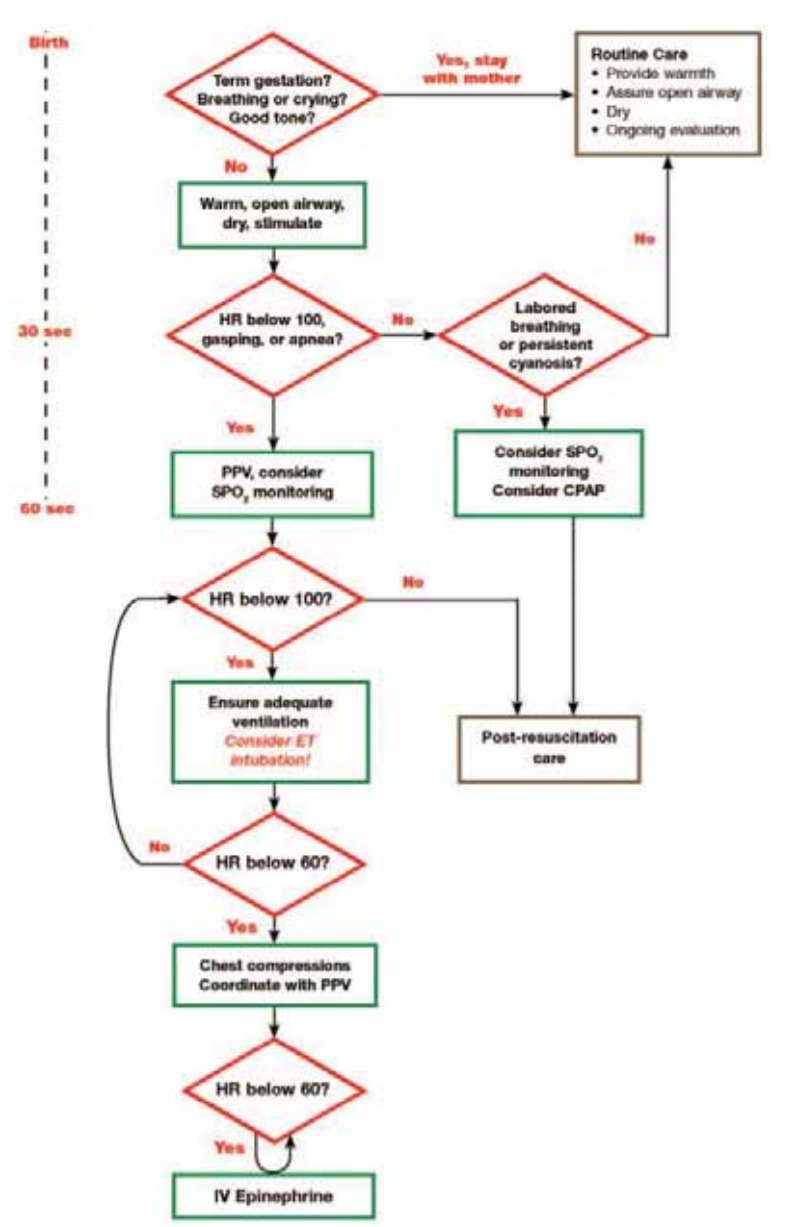

Figure 4: International Liaison Committee on Resuscitation action plan for newborn resuscitation. Source: Perlman et al., (2015)

1.6.3 Helping Babies Breathe programme

The science of newborn resuscitation has undergone a dramatic change since the early 1920s. The emerging of neonatal intensive care units (NICU) in the mid-1970s led to the need for educational programmes to guide newborn care in NICUs. The Neonatal Resuscitation Program (NRP) was then launched in the late 1980s to train and equip care providers with the necessary skills to help newborns during the transition period. The NRP was quickly adopted in America and Europe. However, by the end of the 2000s, many low-income countries were still faced with challenges in newborn resuscitation, including inadequate knowledge and skills and unavailability of equipment (57). It was postulated at that time that establishing the NRP at facility-level in low-and middle-income countries could avert up to 30% of intrapartum-related neonatal deaths (58).

With this in mind, in 2009, the American Academy of Paediatrics, together with its partners, developed the Helping Babies Breathe (HBB) programme – a simple training algorithm that is tailored to low-income settings (59). The training programme considered the possibility that a single provider could be caring for the baby and the mother at the same time. The algorithm was a simplified version of the NRP, however, it did not include chest compressions, medication, or intubation. Instead, it focused on initial stimulation within the first 30 seconds, and assisted ventilation within the 'Golden Minute®', if required. Through the HBB programme, providers are taught how to assess rises in the chest and to feel the umbilical cord to assess HR. The course material consists of

mainly pictorial illustrations and the action plan is colour-coded to signify the level of care (Figure 5).

The HBB programme was initially piloted in 8 Tanzanian sites, including the Haydom Lutheran Hospital in the Manyara region. Since then, more than 15,000 providers have been trained in Tanzania, and approximately 500,000 have been trained worldwide. The HBB programme shows evidence of reductions in both early neonatal mortality and fresh stillbirths in Tanzania, as well as across other low-income countries (54,60,61).

However, studies that followed the implementation of the HBB programme indicated deterioration in skills after training. In Tanzania, it was noted that 1 training day was sufficient to improve the simulation skills of the providers, but these skills could not be replicated in a clinical environment (62). Other sites also saw the same trend of diminishing skills over time (63). Furthermore, it was also difficult for providers to follow the HBB guidelines correctly. Initiating ventilation within the Golden Minute® seemed to be an unattainable goal; unnecessary suctioning and pauses during ventilation were also common (49,50). The concept of frequent training sessions accompanied by quality improvement measures was later found to be necessary for the retention of skills, improved clinical performance, and improved patient outcomes (61,64). These concepts have already been incorporated into the updated HBB programme because, without adequate and sustained quality

improvement measures and adequate frequent training, providers are likely to lose their skills over time (65).

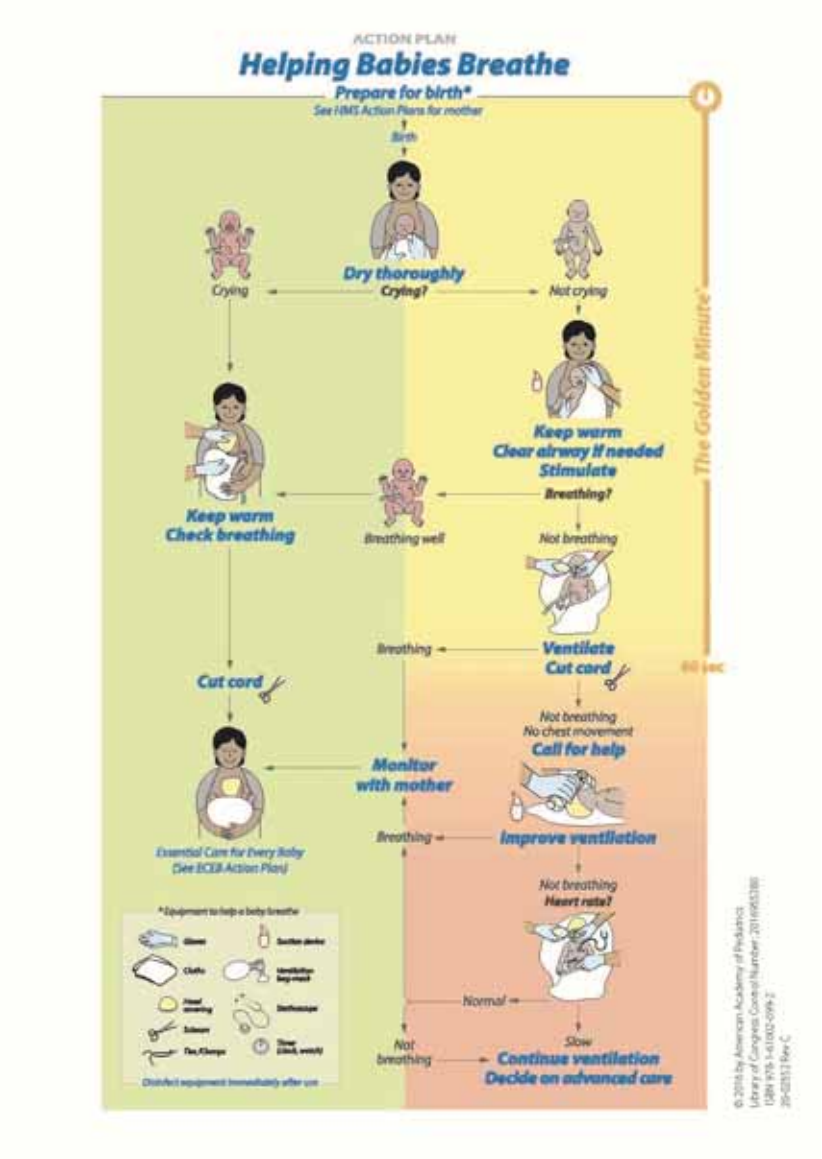

Figure 5: The Helping Babies Breathe action plan, second edition. Source: American Academy of Paediatrics

1.7 Challenges in providing positive pressure ventilation (PPV)

The first important step in providing effective PPV is rapid identification of those who need assistance to breathe. Providers must decide, within 30 seconds of birth, whether ventilation is needed, cut the cord, move the infant to the resuscitation table, and then begin ventilation within 60 seconds of birth. The HBB algorithm instructs the providers to ventilate continuously for one minute, before HR is checked, and preferably the HR should be checked without interrupting ventilation. Providers must ventilate at a frequency of 40–60 breaths/minute. Thus, uninterrupted ventilation of 40–60 breaths/minute until the baby begins to breathe is recommended. Additionally, an inspiration tidal volume of 4–8 ml/kg is believed to be adequate during PPV (66,67), as a volume greater than 8 ml/kg has been associated with lung injury. Recently, Linde et al. (2017) showed that a minimum tidal volume of 6 ml/kg was required to provide a positive change in HR, and a volume of 9 ml/kg was associated with rapid increase in HR, signifying establishment of FRC (68). Furthermore, in the same study, interrupted sequences of PPV were associated with an increased likelihood of death within 24 hours.

PPV skills can be difficult to learn, requiring repeated practice to perfect and maintain the skills. Several studies have reported a significant drop in knowledge and skills 3–6 months after training (69–73). Furthermore, retaining skills after training did not guarantee improved clinical practice (74) or improved clinical outcomes (62). Previous studies have indicated

that the inability to identify those who need assistance, delays in initiating PPV, and the inability to administer effective ventilation are contributing factors to increased intrapartum-related neonatal deaths (50,75). At Haydom Hospital, before-and-after observational studies conducted following the introduction of HBB revealed that the outcomes of neonates who received PPV did not change, and that deaths after PPV were common (50,64). However, the quality of PPV had not been assessed until that point. This was one of the main reasons for the establishment of the Safer Births project (www.saferbirths.com/), where a research device was developed and implemented that could monitor quality of PPV administered to newborns. Moreover, adherence to HBB guidelines were also reported to be a challenge (74). The reason for poor adherence could be due to lack of training competence, but also because of human factors that play a part in a complex and demanding environment such as resuscitation, which had not previously been adequately studied in this setting.

1.8 The Safer Births Project

In 2013, a research, development and implementation project to improve FHR monitoring and newborn resuscitation was initiated at Haydom Hospital and later in other 3 Tanzanian sites. The project was inspired by the initial findings of the HBB programme that was piloted at Haydom Hospital and at other Tanzanian sites. As the name of the project suggests, the major aims were to create new knowledge and develop innovative solutions to better train and equip midwives with the

necessary knowledge and skills while easing their workload to support safer delivery and improve newborn outcomes.

The project was divided into two main domains. The first was to improve FHR monitoring, and the second was to improve newborn resuscitation training and practices. In order to achieve these broad aims, a comprehensive research infrastructure was established involving observations during labour and delivery, 24 hours a day.

Since 2013, full HBB training sessions have been conducted twice yearly at Haydom Hospital, mainly due to the high turn-over of providers. Furthermore, midwives were given easy access to two newborn manikins and a bag and mask specifically reserved for short, regular self-training sessions to emphasize the correct ventilation technique. Moreover, because of the multiple sub-studies within the Safer Births project, it was mandatory for midwives to complete various different training programmes before the hospital initiated any new study.

Data collection for the Safer Births project started in 2013, and multiple types of data were collected through data collection forms, video recordings of all resuscitations, and signal data obtained through newborn resuscitation monitors. This PhD thesis was part of the Safer Births project, with a specific focus on PPV and newborn outcome within the first 7 days of life among newborns delivered at Haydom Hospital. Previous studies conducted at the same site with different objectives, including the evaluation of different types of bag and mask equipment, had their main endpoints at 24 hours of life (68,76).

The Safer Births project has made a tremendous contribution to Haydom Hospital, including the raising of the standards of practice for labour and delivery in this rural hospital. The project activities have also contributed to a gradual decrease in perinatal mortality, starting with the initiation of the HBB programme (77).

1.9 Tanzanian Health System

The United Republic of Tanzania was formed in 1964 by two Sovereign States, Tanganyika and The Republic of Zanzibar. It is a large country in east Africa, covering 945,000 km^2. The United Republic of Tanzania is a unitary republic composed of 31 regions. The population is estimated to be 54.2 million (78). Selected healthcare indicators are presented in Table 2.

Tanzania consists of a pyramidal heath system, with primary healthcare facilities at the bottom and referral health facilities at the top of the pyramid. Primary healthcare facilities include health centres, dispensaries, and community health posts. Referral facilities include district, regional, zonal, and national referral hospitals. The health system also accommodates privately owned facilities, many of which operate as faith-based organizations. Under the public-private partnership agreement, these private facilities provide services as designated district hospitals. In 2018, health expenditure was 7% of the total national budget, which is below the 15% Abuja declaration target (79). The Tanzanian Health system is funded mainly through the government itself (taxation) (21%), donor funding (48%), health

insurance revenue (3%), and out-of-pocket contributions (direct payment during access of services) (25%) (80).

Table 2 – Summary of the Healthcare indicators in Tanzania

Health indicators	2015/16 estimates
Population	54.2 million
Population growth	2.75
Fertility rate	5.2/woman
Life expectancy (male and female)	62.5 years
Maternal mortality	552/100000
Under-five mortality	57/1000
Infant mortality	43/1000
Neonatal mortality	21/1000
Health expenditures: percentage of GDP (2014)	5.60%
Workforce density (physicians, nurses, midwives per 10,000 population	5

Reducing maternal and newborn mortality requires a functioning health system with good quality of care around the time of birth (81,82). In Tanzania, several national policies, strategies, and programmes are in place to address reproductive, maternal, newborn, and child health. Of these policies, the Health Sector Strategic Plan IV 2015–2020 aims to provide basic health and social services that are of good quality,

equitable, accessible, affordable, sustainable and gender sensitive (83). The health sector's strategic plan provides guidance on improving the quality of health services through equal distribution of skilled health workers at a primary level and equitable access to health services among other targets.

In Tanzania, only 65% of women are reported to deliver in healthcare facilities (3). The National Strategic Road Map to Improve Reproduction, Maternal, Newborn, Child and Adolescent health in Tanzania was introduced in 2016 (84). The strategy highlights key interventions that are geared towards improving reproductive health. Some of the interventions that are associated with improving intrapartum-related complications highlighted in this strategy include basic emergency, obstetric, and newborn care, comprehensive emergency obstetric care, skilled birth attendants, and essential newborn care services. The plan aims to reduce maternal mortality from 556 to 292 per 100,000 live births, neonatal mortality from 21 to 16 per 1000 live births, and under-5 mortality from 54 to 40 per 1000 live births by 2020.

1.10 WHO framework for improving maternal and newborn care

The work of this thesis has been built around the WHO quality of care framework for improving the quality of maternal and newborn care in health facilities. The framework was built on the evidence that high

quality care, to manage and prevent complications during labour, childbirth and the immediate postnatal period, is likely to significantly reduce the number of maternal deaths, stillbirths, and early neonatal deaths (48). The framework emphasizes the functioning of the health system as a structure that facilitates the actual process of service delivery in order to obtain better health outcomes. One of the standard statements in this framework states: 'The skilled birth attendants and support staff must have appropriate competence and skills to meet requirements during labour, childbirth, and the early postnatal period'. Thus, the WHO quality of care framework (Figure 6) was chosen as a base on which to explore the quality of care offered by midwives during resuscitation, ways to improve resuscitation practices, and to explore major contributors to newborn mortality in this setting (85).

As I have highlighted in the previous sections, the majority of newborn deaths occur within the first 7 days. Apart from these deaths being directly linked to events in the intrapartum period, poor quality of care is likely a significant additional contributor to death. The WHO introduced several interventions that all newborns should receive immediately after birth. These interventions include immediate skin-to-skin contact to improve thermal control, initiation of breastfeeding within 1 hour, cord care, and eye care (86,87). However, sick newborns, such as those who receive PPV, and premature newborns should receive further specialized care to improve their chance of survival. If not, the delivery room resuscitation efforts will prove ineffective. Monitoring breathing, adequate oxygenation, thermal control, and maintaining glucose and

fluid homeostasis are just some of the important parameters that should be observed post-resuscitation to avoid increased mortality (88–90).

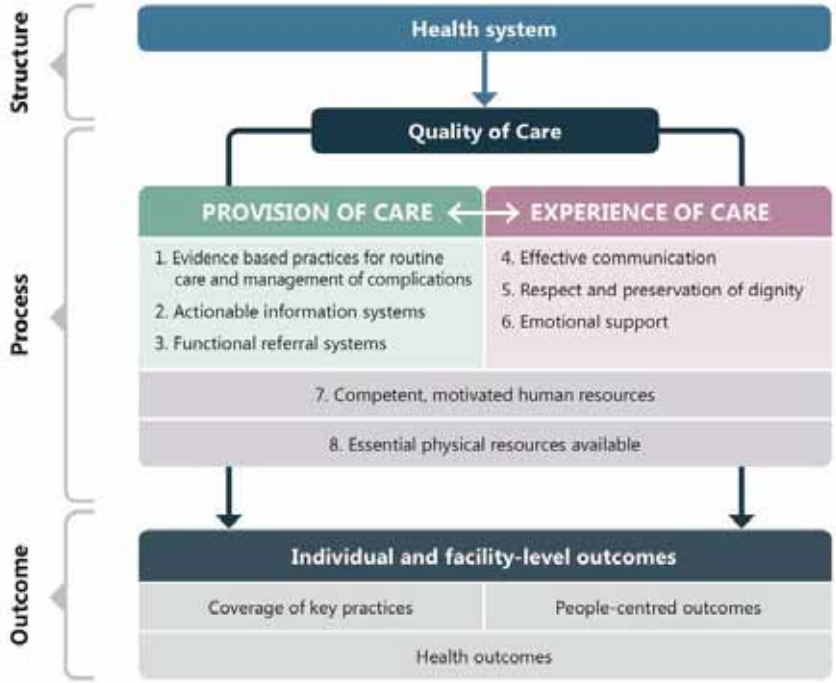

Figure 6: A framework for improving maternal and newborn care. Source: Tunçalp et al. (2015)

1.11 Statement of the problem and rationale for the project

The burden of newborn mortality in Tanzania is significant. Available estimates report approximately 40,000 newborn deaths each year in Tanzania, primarily as a result of intrapartum-related neonatal deaths, prematurity-related complications, and sepsis. One of the identified

interventions with the potential to alleviate intrapartum-related complications is improved quality of care during labour and delivery. However, the challenges that low-income countries are faced with include high levels of unskilled workers, coupled with suboptimal care during labour and delivery.

One of the initial prerequisites for the implementation of any programme is to have an idea of the burden of the problem itself. With great variation in neonatal mortality within and between Tanzanian regions and facilities, obtaining specific mortality rates, including the causes and pathways leading to death, become important for local implementation. In addition, challenges and sub-optimal PPV provision, as discussed previously, could also contribute to increased mortality.

Additionally, previous studies in the area of newborn resuscitation that explored resuscitation practices have been conducted mainly using quantitative methods. Few studies have looked at the midwives' perspective in terms of what factors could improve or hinder resuscitation practice, including the addressing of the subject of human factors and interactions during resuscitation. This is important, because the HBB programme was initially tailored to single providers in low-resource settings. However, at Haydom, two or more providers were noted to be available during newborn resuscitation.

We therefore sought to determine the magnitude of newborn mortality at Haydom Hospital and the major pathways leading to deaths in this remote area. Additionally, we wanted to study a group of newborns who

received PPV and to determine the quality of PPV and factors affecting PPV delivery in this setting.

1.12 Summary

The contribution of intrapartum-related neonatal deaths to newborn mortality rates in Tanzania is significant, accounting for 3 out of 10 newborn deaths. One of the identified interventions that have the potential to alleviate intrapartum-related complications is improved quality of care during labour and delivery. Specifically, during the immediate post-delivery period, newborns who receive PPV are at a greater risk of dying compared to those who receive only basic stabilization. On the other hand, multiple studies have reported poor retention of skills after resuscitation training, posing a question as to whether PPV is provided optimally during the actual practice of resuscitation. The Safer Births project provided an opportunity to study PPV in detail, including the assessment of the 7-day outcomes of newborns in relation to delivery room interventions. It is our hope that the results of this project will help to improve the care of newborns during labour, delivery, and in the postnatal period and, ultimately, contribute to reducing the mortality rate for this and other similar settings.

2 Aims

The aim of this thesis was to describe presumed causes of death among admitted newborns after birth in a rural setting, and to explore resuscitation interventions, barriers, and facilitators that potentially affect early newborn outcomes of either death or survival.

2.1 Specific objectives

1. To describe the presumed causes of death and potential pathways contributing to newborn mortality within 7 days of birth in a rural hospital setting (Study I).
2. To describe perinatal predictors of death, including the quality of PPV administration in admitted newborns (Study II).
3. To explore midwives' opinions on the barriers and facilitators to newborn resuscitation, including PPV, in rural Tanzania (Study III).

2.2 Research questions

In a rural Tanzanian hospital:

1. What are the predominant causes of newborn mortality in this specific rural setting? (Study I)
2. Is the quality of PPV (delivered tidal volume) associated with outcome of admitted newborns during the first 7 days? (Study II)

3. What are the midwives' opinions about barriers and facilitators for newborn resuscitation and ventilation? (Study III)

3 Methodology

3.1 Study setting

The Manyara region is one of Tanzania's 31 administrative regions (Figure 7). It has a population of 1.4 million inhabitants with an annual population growth of 3.2% (91). The 44,522 km^2 region has four hospitals. Haydom Hospital, owned by the Lutheran church, is the central hub for the Haydom Township, with approximately 20,000 inhabitants. The immediate catchment area includes about half a million people with a higher reference area covering 2 million people. The community around Haydom Hospital is mostly low-income. Haydom Hospital offers both reproductive and child health services, such as routine immunization and outreach clinics for pregnant women and under-five children. The hospital itself has a capacity of 450 beds.

The maternity block at Haydom Hospital houses the labour ward, postnatal ward, and the neonatal area. Haydom has approximately 4500 annual deliveries, equating to roughly 53% of deliveries occurring in the catchment area. Less than 10% of women give birth in other facilities, and the remainder give birth at home (92). The hospital provides emergency obstetric services, 24 hours a day, with a caesarean section rate of 22% (93). Midwives work in three shifts. They conduct birthing procedures and newborn resuscitation with a midwife–patient ratio of 1:8. Intermittent FHR monitoring is the preferred method for monitoring FHR during labour using a Pinard stethoscope or hand-held Doppler.

During the study period of this thesis, other concurrent studies evaluating methods of FHR monitoring were taking place. The normal FHR range is regarded as being 120–160 beats/min according to Tanzanian national guidelines, and these were the reference ranges used in this study.

Figure 7: Map of Tanzania showing the Manyara Region and Haydom Lutheran Hospital. Source: Internet

All labour rooms and theatres have a resuscitation table in the corner of the room. The rooms are kept warm by closing the windows. No radiant warmer is available in the labour ward or theatre. Newborns are kept warm mainly by drying followed by wrapping them with a khanga (a piece of cloth that is commonly used in Tanzania). Midwives are taught to use chest rises and changes in HR to confirm air entry into the lungs and as a guide to improve their resuscitation efforts. Oxygen saturation was not monitored, and all resuscitations were undertaken with room air.

The neonatal unit, located within the maternity block, is approximately 20 ft from the labour ward and has a separate team of nursing staff working in a 3-shift rotation (nurse–patient ratio of 1:7). The unit accommodates 10–15 newborns at a time. At the beginning of the study, the neonatal unit consisted of two simple rooms that were later improved in 2017 by modifying these to 3 three separate rooms to accommodate preterm, presumed septic, and asphyxiated newborns. One general practitioner in charge of the neonatal unit, assisted by intern doctors, was responsible for the care of newborns in the neonatal unit. In October 2016, a local paediatrician was recruited and has been in charge of the neonatal unit since then. The unit admits both inborns and outborns. The majority of admitted outborns are home-delivered preterm newborns and referrals from other health facilities, mainly due to intrapartum-related complications and prematurity. Admission criteria include prematurity (<37 weeks), a 5-minute Apgar score <7, fever (>38 ^{O}C), and signs of

respiratory compromise, i.e., inter-costal, sub-costal retractions, or grunting. A newborn can also be admitted for observation for the initial 24 hours after birth. Premature newborns <1500 g are nursed under a shared radiant warmer and the rest are nursed in locally made 'baby cots' (Photo 1). Interventions offered include intravenous fluids, intravenous antibiotics, oxygen therapy using oxygen concentrators, and phototherapy. Stable newborns are allowed to breastfeed, however, if the newborn is not able to breastfeed, the mother expresses milk and it is administered via either an orogastric tube or a cup. Stable premature babies of <1800 g are transferred to a 'kangaroo mother care' ward, where they are nursed skin-to-skin until they attain a minimum discharge weight of 1800 g. Mechanical ventilation and continuous positive airway pressure were not available during the study period.

The hospital has a radiology department located approximately 200 m from the neonatal unit. Due to the unavailability of a portable chest x-ray machine, routine chest radiographs are not obtained. Furthermore, only basic laboratory investigations are performed, mainly for haemoglobin and blood grouping and cross matching if a blood transfusion is required. Blood work for complete blood counts and C-reactive protein levels are performed inconsistently due to a lack of stock, making these investigations unsuitable for inclusion in the study.

Photo 1 – Neonatal unit at Haydom Lutheran Hospital (photo by Robert Moshiro)

At Haydom, admitted newborns are separated from their mothers, and therefore, continuous skin-to-skin contact is not possible until they are transferred to the Kangaroo mother care ward or are discharged. Evidence of poor thermal control has also been reported before in this hospital, despite efforts to train health workers on effective measures for temperature control (30). Moreover, the monitoring of sick newborns is performed by pulse oximetry only. Vital statistics (temperature, HR, and oxygen saturation) are recorded twice daily on a monitoring sheet. Two commonly used antibiotic courses at Haydom are a combination of ampicillin and gentamycin or ceftriaxone as second-line treatment. Treatment is mostly initiated on a presumptive basis and, if clinical deterioration is apparent, or non-improvement of clinical signs are noted after 48 hours of first-line treatment, then second-line treatment is commenced.

3.2 Study design

An overview of the studies included in this thesis is presented in Table 3. This PhD study used a combination of both quantitative and qualitative methods, commonly known as a mixed-methods design, to answer our research questions. The mixed-method design model is a procedure for collecting, analysing and eventually integrating data using both quantitative and qualitative methods in a single study or a series of studies (94). A mixed-methods design is employed only when the combining of both qualitative and quantitative data will lead to an understanding that neither of the two methods would be able to generate when used alone (95). In this PhD thesis, the overall aim of using mixed methods was to gain a deeper understanding of what transpires during newborn resuscitation and how we can use the experiences of midwives to improve our resuscitation training programmes. We employed a modified sequential explanatory design, which is a model in which quantitative studies generate knowledge that is enhanced by performing a qualitative study after analysing quantitative data gathered earlier (95) (Figure 8). The first quantitative study (Study I) answered our first research question, which was to describe pathways leading to death and the causes of newborn deaths at Haydom Hospital. The second quantitative study (Study II) answered our second research question; whether the quality of PPV affected the outcome of newborns during the first 7 days. The final and third study (Study III), a qualitative study, was directly linked to Study II, and explored the human factors that may affect resuscitation and ventilation. The qualitative study depended on

the second quantitative study as it was designed to expand on the results of Study II to provide more information about potential factors affecting ventilation and how to best improve resuscitation practices.

During the execution of the three studies, we performed interim analyses after one year of data collection (Study II) and used the results to inform and build the design of the qualitative study. Additionally, the qualitative study integrated additional information generated by other quantitative observational studies conducted earlier at the same site, but with 24-hour mortality as the end point (68,96). As a result, we ultimately carried out the three studies using a modified sequential explanatory mixed methods design.

The decision to integrate the quantitative and qualitative studies occurred during the interpretation of the results. Thus, after the completion of both the quantitative and the qualitative studies, separate analyses were conducted, and the three studies were discussed together and the data merged to answer the aim of this thesis.

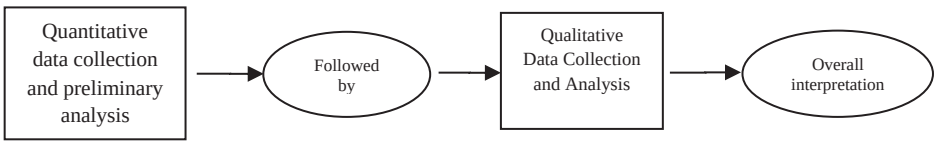

Figure 8: Modified sequential explanatory mixed methods design (designed by Robert Moshiro)

Table 3: Overview of the 3 studies in the thesis

Sub-studies	Design	Focus	Participants	Data collection method	Analysis

Study 1	Observational study (quantitative)	Causes and pathways leading to death	Mothers and newborns who delivered at Haydom	Observational using a data collection form	Descriptive statistics, Chi-square test, Mann–Whitney *U* test, regression analysis
Study 2	Observational study (quantitative)	Perinatal and ventilation factors associated with death	Newborns resuscitated in the delivery room and admitted	Observational using a data collection form and a newborn resuscitation monitor*	Descriptive statistics, Chi-square test, Mann–Whitney *U* test, regression analysis
Study 3	Qualitative study	Explore barriers and facilitators of newborn resuscitation	Midwives who conduct births and resuscitation at Haydom	In-depth interviews	Qualitative content analysis

*For a description of the Newborn Resuscitation Monitor, see page 51

3.3 Quantitative observational (non-interventional) studies

Study I and Study II were prospective observational clinical studies where all newborns who were delivered at Haydom Hospital and thereafter admitted to the neonatal unit were recruited between October 2014 and July 2017. The timeline of the studies conducted and the

inclusion and exclusion criteria are presented in Table 4 and Table 5, respectively. Included newborns were then followed to determine their outcomes at 7 days (Studies I and II).

Table 4: Timeline of all studies in this PhD

	2014				2015				2016				2017			
Quarter of the year	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Study I																
Study II																
Study III																

For Study I, we performed an estimation of the required sample size based on the early neonatal mortality of 11 per 1000 live births at Haydom Hospital in 2013. We estimated that 2 years of data collection would provide a sample size of 100 deaths that would be considered sufficient to describe the causes of death with acceptable error margins. However, due to an improvement in early neonatal mortality during the course of the study (77), the data collection period was extended for approximately 9 months to include enough data for analysis. For Study II, duration of time for HR to increase to >100 bpm was considered the best indicator to study the effectiveness of ventilation. However, we did not have all of the information that was required to calculate a sufficient sample size at the beginning of the study. Therefore, we began data collection and the sample size was calculated at a later stage (4 months afterwards). Based on the previously collected data, the standard deviation for HR to increase above 100 bpm was 30 seconds and 65 seconds between those who survived and those who died, respectively.

With these numbers, a power calculation, based on a *t*-test, indicated that, for a total sample size of 100 newborns with an initial HR <100 bpm at the start of ventilation, the power to detect a difference of 30 seconds (from start of ventilation to reach HR >100 bpm among newborns with initial HR <100 bpm) was 91%. For the Mann–Whitney *U* test, which was necessary because the data were not normally distributed, the power was a bit lower; at worst 15% lower, implying that we would achieve power of at least around 80% with a sample size of 100.

Table 5 – Inclusion and exclusion criteria for Study I and Study II

Study	Inclusion criteria	Exclusion criteria
Study I	All newborns who were delivered and then admitted to the neonatal unit during the study period	1. All newborns who were delivered and stayed with the mother in the post-natal ward 2. Newborns who died within 30 min in the labour ward
Study II	All newborns who received PPV and were then admitted to the neonatal unit	1. Newborns who were not admitted following PPV in the labour ward 2. Newborns who died within 30 min in the labour ward

3.3.1 Study procedures

3.3.1.1 Training of relevant clinical staff

Before the commencement of the studies, all nurses working in the neonatal unit were given a short training session on essential newborn

care, including the monitoring of newborns who were admitted. The training also served as part of the hospital clinical improvement programme. This involved updating the healthcare workers on different treatment protocols and procedures. The training was conducted twice yearly by a PhD student (RM) together with other members of the research team. Training, related to the Safer Births programme, on newborn resuscitation started in 2011, as stated previously. Midwives were trained in the HBB programme (59) with short ventilation training sessions conducted on a weekly basis and full HBB refresher training twice yearly, as previously stated. RM was the primary local HBB trainer, together with three nurses who were also involved in the training of other midwives and theatre nurses during the implementation of the HBB.

3.3.1.2 Data collection and management

Observational data

After the Safer Births programme was instigated in 2013, several research assistants (*n*=14) were identified and trained to observe and document every delivery in the labour ward and theatre. The research assistants, who have no medical background, were purely observers and were not allowed to interfere with any procedure or intervention. They recorded their observations on a standard Safer Births data collection form (Appendix 1). The research assistants were available 24 hours a day in a 3-shift rotation. Research assistants used stopwatches to record variables which required timing, such as duration of time from

ventilation to breathing. FHR was measured by the attending midwife by auscultation using a Pinard stethoscope, handheld Doppler, or continuous Doppler. Moreover, all resuscitations were video-recorded for the purpose of quality improvement and to better understand the information recorded by a newborn resuscitation monitor (NRM). The characteristics of admitted newborns and information collected during admission in the neonatal area were collected using a separate "Neonatal Room" data collection form (Appendix 2). Admitted newborns were followed for the initial 7 days.

Signal data

HR and ventilation parameters were recorded using an NRM (Laerdal Global health, Stavanger, Norway) (Figure 9) (49). The NRM was certified and met European standards for patient safety (CE marked). The monitor was installed in all delivery rooms and mounted on the wall in front of the resuscitation table for the provider to see the displayed HR (Photo 2). The monitor had sensors capable of synchronously recording HR, airway pressure, ventilation parameters such as flow and volume, and expired carbon dioxide. Ventilation flow and volume (inspiratory and expiratory) were measured using a flow sensor (MIM Gmbh, Krugzell, Germany) placed between the self-inflating bag and mask. The sensor had negligible flow resistance and dead space (1 ml) and measured airflow using hot wire anemometer technology. Mask leakage was calculated (volume was also calculated based on flow) by the difference between the inspiratory and expiratory volumes. The bag and

mask used was a standard newborn bag and mask or an upright bag and mask without positive end-expiratory pressure (Laerdal Global Health, Stavanger, Norway) (76) (Figure 10).

Photo 2: Newborn resuscitation monitor mounted on the wall in front and above the resuscitation table (photo by Robert Moshiro)

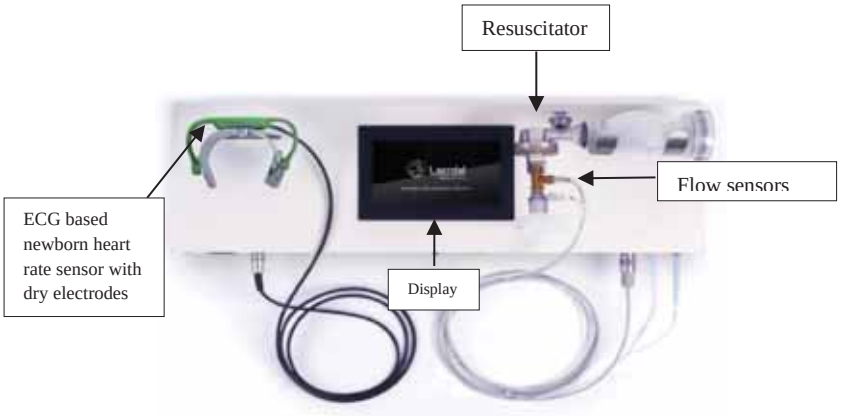

Figure 9: Newborn resuscitation monitor (figure courtesy of Laerdal Global Health)

Figure 10: Standard and an upright bag and mask (figure courtesy of Laerdal Global Health)

HR was calculated from electrocardiogram (ECG) recordings measured by dry electrodes. The ECG was recorded and HR calculated using a proprietary algorithm based on a zero crossing count algorithm (97). The dry-electrode ECG technology and HR algorithm were validated (by the manufacturer) on human subjects against HRs measured on the industry standard equipment, a Philips HeartStart MRx Monitor/Defibrillator (Philips Healthcare, Andover, MA). The HR sensors incorporated an accelerometer to record any movement that might indicate possible ECG signal disturbance. The HR sensor was then connected to the display screen by a cable. The HR displays functioned to provide the midwife continuous HR feedback during resuscitation. Data from all sensors were stored in an internal memory card and could be downloaded to a computer through a USB connection.

Whenever resuscitation was required, a midwife would perform the initial stabilization by drying, stimulation and/or suctioning, as instructed by the HBB guidelines. If the midwife decided that

resuscitation was necessary, the cord was separated, and the newborn moved to the resuscitation table. The NRM HR sensor was then fitted around the abdomen before ventilation commenced with a bag and mask attached to the NRM. The application of the ECG-based sensors was noted to take an average of 3 seconds to complete, and a HR was detected within approximately 5 seconds (49). The time from birth to decision to ventilate, and hence application of ECG sensors, varied between patients. Time in seconds for HR to reach 100 bpm and expired tidal volume, was downloaded from the NRM and extracted using Q-CPR Review 3.1.2.2 (Laerdal Medical, Stavanger, Norway). Figure 11 represents an example of a volume signal as extracted by Q-CPR Review.

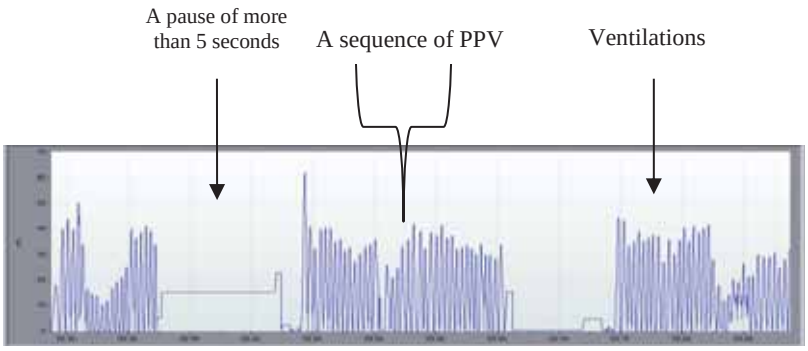

Figure 11: Volume signal output from newborn resuscitation monitor (diagram by Robert Moshiro)

Selection of variables to be used in the analyses

Study I

The Safer Births data collection form was initially developed in 2013 and underwent several amendments to accommodate different studies that commenced at different time points. Study I utilised variables drawn from the Safer Births form that would help to reveal pathways for causes of deaths, such as FHR during labour, amniotic fluid characteristic, PPV at birth, and Apgar score. We also included baseline characteristics, such as gestational age, mode of delivery, birth weight, gender, and gestational age. In this study, signal data were excluded. In addition, we developed a second form for the purpose of collecting information during the 7 days of follow-up in the neonatal area.

Study II

In addition to the variables that were used in Study I, Study II included time variables in the labour ward and ventilation parameters that were recorded by the newborn resuscitation monitor. The time variables, such as start and end of PPV, were important, as they helped us to understand and interpret the data from the newborn resuscitation monitor. Ventilation parameters to be analysed were selected based on parameters used in previous studies in the same setting, the findings from these studies, and parameters planned for future studies.

Data management

Data from the data collection forms were double-entered using EpiData 3.1 (EpiData Association, Odense, Denmark) into computers by two different trained data clerks, and then crosschecked immediately for discrepancies. The research manager, Estomih Mduma, was responsible

for supervising data collection and the data entry systems. In addition, I verified all of the information that was collected and entered for consistency.

Recorded resuscitations were downloaded and matched with a Safer Births data collection form based on the date, time of resuscitation, and the monitor used. The Safer Births form (Appendix 1) was then matched by clinical information drawn from the "Neonatal Room" form (Appendix 2). A standard operating procedure was developed for the sole purpose of guiding a matching process. If the resuscitation episodes failed to match with the variables on the Safer Births data collection form, the recorded resuscitation was then discarded. Furthermore, all of the signal data included in this PhD project were proofread by a team of researchers to ensure the inclusion of the episodes with minimal discrepancies. I also verified all of the episodes manually using the Q-CPR Review 3.1.2.2 (Laerdal Medical, Stavanger, Norway) software application. Any signal data that were not clearly understood were cross-checked against the video data record of the same episode. Ventilation parameters, including HR signals, were extracted from the Q-CPR review and merged into an SPSS database. The original data were secured in the database at Haydom Hospital and a copy of all data, including matched resuscitation episodes, were uploaded onto a dedicated Safer Births server that only researchers with clearance were able access.

3.3.2 Data analysis

Analyses of the quantitative observational data (Studies I and II) involved variables from the Safer Births data collection form, signal data from the NRM, and data gathered from the newborn unit. Categorical data were summarized as numbers and percentages, and continuous data as means and standard deviations (SD) or medians and interquartile ranges (IQR), as appropriate. Chi-square tests were used to test for differences in categorical variables, and Mann–Whitney *U* or *t*-tests, as appropriate, were used to test for differences in continuous variables after testing for normality using the Shapiro-Wilk test. Multivariable logistic regression analysis was used to model how various variables influenced the risk of death. Variables with a *p*-value <0.20 in the univariable analyses were included in the multivariable analysis using a stepwise backward elimination method, with the retention of predictors with *p*-value <0.05. In the final step, eliminated variables where re-entered into the model one-by-one and kept if $p<0.05$. The results are presented as odds ratio (OR) with 95% confidence intervals (CIs). We could not include variables obtained during admission due to missing information as regression analyses were performed with complete cases. Variables obtained during the initial assessment upon admission were therefore entered into a separate model. Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, N.Y. USA). Variables used in both Study I and Study II are summarized in Table 6.

Table 6: Variables included in Study I and Study II

Variable	Values/units of measure	Study I	Study II
Primary outcome			
Neonatal outcome at 7 days	Dead, Alive	√	
Time to achieve heart rate >100	Seconds		√
Secondary outcomes			
Presumed causes of death	Birth asphyxia, prematurity, sepsis, meconium aspiration syndrome, congenital abnormalities	√	
Foetal heart rate during labour	Normal, abnormal/not detected, not measured	√	√
Amniotic fluid colour	Normal, meconium stained, blood stained	√	√
PPV attempted	Yes, No		√
Apgar score	Low (<7), Normal (≥7)	√	√
Heart rate at the start of ventilation	<100 bpm, ≥100 bpm		
Median time for heart rate to raise above 100 bpm	Seconds		√
Medium ventilation volume	Millilitres per minute		√
Median time from birth to start PPV	Seconds		
Median number of ventilations before reaching 6 ml/kg	Number		√
Median ventilation frequency during first 60 seconds	Seconds		√
Baseline characteristics			
Birth weight	Grams	√	√
Gestational age	Weeks	√	√
Antenatal care attendance	Yes, No	√	√
Mode of delivery	Spontaneous vertex delivery, Caesarean section	√	√

Gender	Male, female	√	√
Oxygen saturation on admission	Percentage	√	
Initial assessment on admission		√	√
Temperature	Degree Celcius		
Heart rate	Beats per minute		
Need for oxygen therapy	Yes, No		
Random blood glucose	Millimole per litre		

PPV, positive pressure ventilation; bpm, beats per minute

3.4 Qualitative study design

Individual, semi-structured interviews with midwives who are responsible for managing deliveries and newborn resuscitations at Haydom Hospital were conducted and recorded using a digital audio recorder. Individual interviews were chosen because they allow for insight into people's thoughts, feelings, and behaviours (98). This was also determined to be the best method for exploring their individual experiences, beliefs, and behaviours about newborn resuscitation, an important and lifesaving procedure. To ensure maximum variation, the selection of the individual interview participants was based on the number of years spent working in the maternity/labour ward and the number of babies resuscitated during the same period. Haydom Hospital, being a rural hospital, has a high turnover of young midwives. There is a good mixture of midwives who have settled in the area and have more than 10–15 years' working experience, with younger midwives having less experience. A total of 18 midwives were working in the hospital at

the time of the interviews. Because the objective of this qualitative study was to obtain a deeper understanding of ventilation and resuscitation practices, we set a minimum criteria of including those who had worked in the labour ward for at least one year and those who had conducted at least three resuscitations by that time. This ensured inclusion of information-rich informants (99). During the actual recruitment process, I first approached midwives with many years of experience and invited them to participate in the initial individual interviews. These were older midwives who had been in practice for more than 10 years. Midwives with 2–5 years of practice were also invited, resulting in a balance of interviewees with an average of 8 years of experience (Table 7).

Table 7: Profile of the midwives who participated in the study

Participant	Age	Sex	Experience (years)
1	28	Female	4
2	47	Female	18
3	36	Female	7
4	34	Female	7
5	26	Female	2
6	36	Female	13
7	28	Female	4
8	30	Female	5

Participants were informed about the study and asked for their permission to be interviewed. Once permission had been granted, the

interview sessions were conducted within the hospital premises, in a private office, and at a time convenient to the participant. Participants were asked to sign a consent form before taking part in the interview. The questions for the interview guide (Appendix 3) were developed based on the observations that were made during the initial analysis of quantitative resuscitation data (Study II) and previously generated data. The initial analysis of the Study II data revealed delayed initiation of ventilation with an average time from birth to start of ventilation at close to 2 minutes, as opposed to the recommended one minute timeline termed the "Golden Minute®". Interruption during ventilation was also common, indicating that the midwives were not following the resuscitation protocol. Efforts to address interruption had already begun through previous training sessions. We therefore developed the first draft of the interview guide with questions under the following headings: communication and cooperation during resuscitation; initiation of ventilation; continuation of ventilation; resuscitation training; resuscitation protocol; and resuscitation monitoring. The interview guide was initially shared among researchers working on the Safer Births study who were experts in newborn resuscitation for further enhancement. The interview guide was then piloted with one midwife working in the labour ward. This pilot interview helped to modify the language used in the questions for clarity. Key questions were followed by probes, depending on the flow of the interview, to prompt the interviewee further and obtain a deeper understanding of the topic. The pilot interview was not included

in the final analysis. The final interview guide was then used to interview 8 midwives between December 2015 and January 2016.

I conducted the initial two interviews for the purpose of gaining experience in qualitative interviewing, and the rest of the interviews were conducted by one research assistant (SM) who holds a Bachelor in Clinical Psychology. SM was working as a psychologist in a mental health unit at Haydom Hospital and knew the study site very well, having worked at Haydom for 2 years. However, he had no previous experience of performing qualitative interviews or conducting qualitative research. After familiarising himself with the study protocol and aims of the study, we reviewed the interview guide together and discussed each of the questions in detail. SM then conducted one pilot interview which was reviewed and by the research team, who approved of his technique. The interviews sessions lasted an average of 40–50 minutes. At the end of each interview day, I met with SM, together with a senior researcher in our group, and we reviewed the information that had been collected. This allowed us to generate an emerging understanding of newborn ventilation practices before the subsequent interview session. This iterative process of data collection and review was used to shape the questions being asked in the subsequent interviews, as well as to recognize the saturation point at which no new information was emerging (99). The interviews were conducted in Swahili and were audio-recorded.

3.4.1 Data analysis

Qualitative data analyses were performed using qualitative content analysis (100). Content analysis allows the analysis of textual data to identify relationships between texts, allowing an understanding of the meaning to emerge, and eventually to summarize the data into categories with similar meanings. The audio recordings were transcribed verbatim by a native Swahili speaker who was not directly involved in this project, but who is a healthcare worker experienced in transcription. Transcripts were then translated into English by the same person to allow researchers who are non-Swahili speakers to understand the materials that have been generated. Each paragraph was translated and positioned below the original Swahili paragraph to preserve the meaning of the whole paragraph. I reviewed all of the transcribed and translated transcripts to ensure that the meaning was maintained and that any minor mistakes were corrected. The transcripts were then read and re-read to identify text relevant to newborn ventilation and resuscitation. Using qualitative content analysis, text containing key thoughts about ventilation and resuscitation was then condensed, abstracted, and labelled with a code (Table 8). The codes were shared and reviewed again by researchers to make sure they indeed captured the meaning of the text represented. Similar codes were grouped to obtain sub-categories, and similar sub-categories were grouped into categories using the constant comparative method (101). During the process of developing sub-categories and categories, emphasis was placed on the original transcripts with minimal interpretation of the text, i.e., the manifest content analysis level, as

explained by Graneheim and Lundman. NVivo 11 software was used to facilitate the generation and sorting of codes.

Table 8: Illustration of how codes, sub-categories and categories were obtained

Interview quote	**Condensed meaning unit**	**Code**	**Sub-category**	**Category**
What helps is the initial preparation, before any delivery we prepare our equipment making sure they function well [RNM2].	Initial preparation of equipment helps	preparation	Preparation of equipment and staff	Proper monitoring of labour and preparation for delivery helps to start ventilation on time
For now it is not difficult since we have it in place, not like in the past where when the baby is born that's when you run to look for it "guys can I have a mask, can I have this" [RNM1]	Nowadays our equipment is located in one place	equipment located in one place		
Sometimes it happens that you deliver another woman in the labour room that it's equipment has already been used without cleaning, it leads to delays in helping another baby [RNM5]	Conducting delivery in a room that has uncleaned equipment	Uncleaned equipment lads to delays starting ventilation		
first thing is to detect a baby who will need resuscitation during monitoring of labour, that the woman is going to deliver soon and there is abnormal fetal heart rate [RNM2]	Early detection of those who need resuscitation using abnormal fetal heart rate	Monitoring of fetal heart rate during labour	Close monitoring of labour to detect problems early	
You will have doubts since she had prolonged second stage, and you wonder if the baby will come out ok, you will have to call for	Calling for assistance due to prolonged second stage	Prepared to do resuscitation after diagnosing fetal distress		

help because you don't know what will happen after delivery [RNM3].				

3.5 Ethical considerations

This thesis was part of the Safer Births project, which obtained ethical approval from the National Institute for Medical Research (NIMR), Tanzania (Ref. NIMR/HQ/R.8a/Vol.IX/1434 and NIMR/HQ/R.8c/Vol. I/325) and the Regional Committee for Medical and Health Research Ethics in Western Norway (Ref. REK 2009/302). All relevant healthcare workers at Haydom Hospital were informed about the Safer Births programme and gave their consent to participate. Women delivering at Haydom Hospital were informed about the Safer Births research. Only those eligible for interventional studies (other studies in the Safer Births project not included in this thesis) were asked for consent.

Midwives who participated in the qualitative study (Study III) were asked to provide signed written consent. The written information, including the consent form, was given to the midwife before the commencement of the interview. Enough time was given to the midwives to read and understand the information, followed by a period where questions and clarifications were addressed, until the interviewee was comfortable with signing the consent form. All of the midwives who were asked to participate in in-depth interviews agreed to do so.

This PhD study was funded by the Norwegian Research Council. The Safer Births project received funding from the Research Council of Norway and the Laerdal Foundation. The study was also sponsored by Haydom Lutheran Hospital, which took all of the responsibility to ensure patient safety and good clinical practice. The Safer Births project was part of the quality improvement initiative at Haydom Hospital and participants did not receive any form of monetary compensation.

4 Summary of Results

4.1 Causes of newborn mortality

This study set out to answer our first research question, which asked what the predominant causes of newborn mortality are in this specific rural setting. This study included a total of 671 newborns who were admitted to the neonatal area between October 2014 and July 2017. A total of 124 (18%) newborns died within 7 days; of these, 61 (49%) died within 24 hours, 38 (31%) died within 72 hours, and 25 (3.7%) died beyond 72 hours of life. The presumed causes of death included birth asphyxia (BA) (*n*=59), complications related to MSAF (*n*=13), prematurity (*n*=19), presumed/suspected infection (*n*=19), and secondary complications related to congenital anomalies (*n*=14).

BA and complications related to MSAF, i.e., intrapartum-related neonatal deaths, were responsible for a total of 72 (54%) deaths within the first 7 days. Delivery was via emergency caesarean section in more than half of the cases in both conditions. PPV was applied in the delivery room in 92% and 69% of those who died of BA and MSAF, respectively. Moderate hypothermia and moderate to severe hypoxia were found in more than 60% in both BA and MSAF cases. Early death (within 24 hours) occurred in 50% of BA and MSAF cases, and, by the end of 72 hours, 90% of newborns had died in both groups.

Prematurity and its subsequent complications contributed to 19 (15%) newborn deaths. This group of newborns had uneventful labours and

delivery room transitions. During admission, moderate hypothermia and severe hypoxia occurred in 74% and 37% of newborns, respectively. Two-thirds died within 72 hours, while only 26% died beyond 72 hours. Presumed sepsis also contributed to 19 (15%) newborn deaths, while 14 (11%) died due to congenital abnormalities.

Characteristics of newborns who died versus characteristics of those who survived were entered into a model to predict the risk of death. An Apgar score <7 at 5 minutes (Adjusted odd ratio (AOR) = 3.20; 95% confidence interval (CI): 1.42;7.22), oxygen saturation on admission (AOR=4.73; 95% CI: 2.02; 11.13) and birth weight (AOR=0.64; 95% CI: 0.48;0.84) were associated with increased odds of death in the final model for all admitted neonates. Temperature was not included in the model due to missing data. We also performed additional analysis of term newborns only (excluding congenital malformations). The odds of dying versus survival increased 4.5-fold (95% CI: 1.40;11.44) (p=0.010) with PPV, 3.6-fold (95% CI: 1.67;7.81) (p=0.006) with a 5-minute Apgar Score <7, and 4.6-fold (95% CI: 1.82;11.65) with an admitted saturation <60%.

4.2 Positive pressure ventilation and outcome of admitted newborns

Study II aimed to answer our second research question on how the quality of delivered tidal volume is associated with the outcomes of admitted newborns. In this study, a total of 514 newborns received PPV. Of these, 232 were admitted and were followed up; 53 (23%) died within

seven days. Of those who died, 15 (28%) died within 24 hours, and 75% died within the initial 72 hours of life.

Of the 232 admitted newborns, 196 had a complete set of ventilation parameters, including expired volume and HR, parameters used as proxies for quality of ventilation (Study II). The HR response of newborns who died took a longer time to reach 100 bpm during PPV compared to those who survived i.e., median 180 seconds versus 149 seconds (p=0.07), respectively, but the difference was not statistically significant. Less volume (ml/kg) was delivered to newborns who died compared to survivors during the first 60 seconds of PPV, i.e., 5 ml/kg versus 6 ml/kg (p=0.13), and more during the whole PPV episode, i.e., 9 ml/kg versus 7 ml/kg (p=0.41), but the difference was not significant (Table 9). It took a longer time to achieve a target volume $V_t \geq 6$ ml/kg for those newborns who died compared to those who survived, i.e., a median value of 14 seconds versus 4 seconds (p=0.008), respectively. However, newborns who died were ventilated for a much longer time compared to survivors, i.e., 402 seconds versus 230 seconds (p=0.001), respectively, and had less mask leakage compared to those who survived (p=0.027) (Table 7).

We conducted multivariable logistic regression analysis to determine which variables could predict an increased risk of death. When adjusted for all variables in the final model, abnormal FHR (AOR=3.15; 95% CI: 1.21;8.19) (p=0.019), HR at the end of PPV (AOR=7.63; 95% CI: 2.05;28.41) (p=0.002), and median duration of PPV (AOR=1.002; 95%

CI: 1.001;1.003) (p=0.001)] were all associated with an increased risk of death.

Table 9: Responses of newborns to positive pressure ventilation in relation to outcome dead vs survived within first 7 days

Variable	Dead *n*=53 Median (IQR)	Survived *n*=179 Median (IQR)	*P*-value
Time from birth to application of HR sensor (s)	116 (73–140)	108 (76–158)	0.52[a]
Time from birth to detection of initial HR (s)	116 (83–152)	113 (85–158)	0.92[a]
Time from birth to start PPV (s)	117 (85–147)	115 (85–147)	0.35[a]
Time from birth to HR increase >100 bpm (s)[c]	180 (119–235)	149 (105–208)	0.07[a]
V_t first 60 s of PPV (ml/kg)	5 (3–10)	6 (4–12)	0.12[a]
V_t whole episode of PPV (ml/kg)	9 (5–14)	8 (5–12)	0.36[a]
Vol/min first 60 s of PPV (ml/min)	781 (375–1414)	896 (429–1528)	0.14[a]
Vol/min whole episode of PPV (ml/min)	1389 (731–1900)	1140 (643–1876)	0.41[a]
Time from start PPV to V_t >6 ml/kg (s)	14 (2–31)	4 (1–18)	0.008[a]
Number of ventilations before >6 ml/kg	7 (2–20)	3 (1–10)	0.006[a]
Time used ventilating during first 60 s (s)	44 (31–54)	40 (28–55)	0.57[a]
PPV frequency during first 60 s (inflations/minute)	50 (40–59)	45 (37–57)	0.19[a]
PPV frequency during whole episode (inflations/minute)	52 (39–60)	44 (36–55)	0.25[a]

Mask leak during ventilation (%)	33 (21–55)	40 (26–54)	0.027[a]
Time of whole episode of PPV (s)	402 (203–785)	230 (104–466)	<0.001[a]

PPV, positive pressure ventilation; Vol/min, volume per minute; s, seconds; HR, heart rate; BPM, beats/minute; V_t, expired tidal volume; IQR, inter-quartile range.

[a]Mann–Whitney *U* tests; [b]Chi-square

All ventilation parameters *n*=196 except [c]median time from birth to HR to increase >100 BPM *n*=127

4.3 Factors affecting ventilation

This qualitative study received inputs from Study II to explore further factors that affect the effective delivery of PPV by the midwives. A total of 8 midwives aged between 26 and 47 years with a median experience of 8 years working in the labour ward were interviewed. Each had performed at least 10 resuscitations before the interview. All the midwives who were interviewed held a diploma in nursing, which is a three-year training programme to become a registered nurse midwife. The level of resuscitation training was almost the same for all midwives, i.e., all had attended a full HBB course (one day of training) at least once. Few had attended multiple HBB courses. None had received advanced resuscitation training such as the Neonatal Resuscitation Program (NRP), which is widely used in high-income countries. Five main categories were identified to affect ventilation practices. First, midwives were of the opinion that increased frequency of self-practice was the key to improving skills and their performance. They agreed that ventilation skills do take time to acquire and thus practice was important. They went further to suggest that improving simulation training and including a

sense of urgency in the simulations was needed. One midwife said: '*if there was a way of improving the manikin so that when we are stimulating there is something that shows you some improvement (...)'*.

The monitoring of labour and preparation for delivery was another main category that was identified to improve ventilation performance. Good monitoring of labour was reported to decrease the need for resuscitation. Midwives were of the opinion that anticipating problems early and preparing resuscitation equipment helped them to start resuscitation on time, if the need arose. Storing resuscitation equipment in one specific place close to the resuscitation table was specifically mentioned as being important for starting ventilation quickly.

Furthermore, effective teamwork and commitment during resuscitation was reported to determine how quickly ventilation could be initiated. Midwives reported that they do call on each other in the event of an emergency, and that they are able to use each other's strengths to help the baby to breathe. Despite this perception, they sometimes do not agree on their roles prior to resuscitation; however, in the presence of two or more midwives, they will give each other ideas and remind each other what has to be done or even let someone who is more experienced perform ventilation. One midwife explained: *'(...) once you see that she is not managing to get air in, then you ask to help her, and what we care about is the life of the baby, therefore you can't keep quiet, you ask her to let another person ventilate'*. Alternatively, midwives shared their experiences of not being organized, leading to confusion, interference

and interruptions in ventilation when resuscitation is attended by more than two midwives. They reported that it is not routine to first agree on the role that each midwife will perform during resuscitation, especially when resuscitation was not anticipated.

Difficulties interpreting clinical signs immediately after delivery were also mentioned as a factor that hinders efforts to start ventilation on time. Midwives reported that they sometime fail to identify those in need of ventilation quickly, and they spend more time stimulating and suctioning hoping the baby will improve. However, by the time they realize the baby is not improving or is worsening, significant time has lapsed. One midwife reflecting on such situations said: *'(…) sometimes you decide that this baby does not have a big problem, it will breathe and cry, like this baby does not have to be resuscitated but after few seconds later, suddenly it changes condition (...)'*

Feelings of fear and anxiety during actual resuscitation were described by the midwives as a reason for not following the HBB guidelines accurately. Midwives reported that they become stressed under the pressure to try to save the life of a human being, as described by one midwife: *'(…) you become fearful thinking whether you will be able to save that life (…) that is why sometimes we do panic'*. Although it is expected that health workers faced with emergencies will be a bit anxious, this can sometimes make them react quickly in an appropriate manner. However, if healthcare workers are not capable of containing their anxiety during such emergencies, this might lead to poor

performance due to an inability to follow best practice guidelines and algorithms, as explained by another midwife: '*Once you have fear, you will not be able to hold it properly (bag and mask) the way we have been instructed to, and you will get air leaks because you are shaking, you have fear, also it will make you not to hold it properly and the baby will not get the air you are giving it'*.

5 General discussion of results

We found that intrapartum-related neonatal deaths contribute significantly to neonatal mortality and constitute a major pathway contributing to death in this rural setting. Other important pathways to death included prematurity, presumed sepsis, and congenital abnormalities. Newborns who died of presumed intrapartum-related causes exhibited more FHR abnormalities in utero, lower initial HR upon delivery, and lower HR following PPV. The median tidal volume delivered during the first 60 seconds of PPV and during the whole episode of PPV did not influence the outcome; neither did the HR responses during PPV. However, newborns who died were slower to respond to PPV compared to survivors. Fear and anxiety about whether the newborn will improve during PPV and difficulties interpreting clinical signs immediately after delivery were identified as factors that affect effective ventilation, such as frequent interruption during PPV and delays in initiating PPV within the first minute. Other factors that were suggested to contribute to ineffective ventilation were a lack of proper training and lack of effective teamwork.

5.1 Presumed causes of newborn deaths and pathways leading to death

The contribution of intrapartum-related neonatal deaths to 7-day newborn mortality in this rural setting was higher than previously reported in Tanzania (2,3,14) and globally (6,9,12). In this study,

intrapartum-related early neonatal deaths, i.e., a combination of BA and complications of MSAF, likely resulted from the interruption of placental blood flow. Mortality due to intrapartum-related neonatal deaths was still high, despite not including deaths that occurred in the delivery room in the analysis. In a recent published report conducted in Asia and Africa, intrapartum-related events or hypoxia-ischemia were found to be the leading cause of newborn deaths, as opposed to prematurity as has been widely reported previously (102). Although this recent report was based on verbal autopsies, the similarity of their estimates to our findings likely reflects previous misclassifications of prematurity-related deaths, which may have actually been intrapartum-related neonatal deaths.

In our study, the diagnosis of BA, in line with the WHO criteria (i.e., a non-breathing baby with a 5 minute Apgar score <7), and complications of MSAF were made clinically, without supportive evidence of severe foetal acidaemia (umbilical cord arterial pH <7.00), multiple organ failure (103), or radiological confirmation. It is well documented that the Apgar score is not accurate in predicting outcome. Its inter-observer variability is also a limitation (104). The primary aim of the Apgar score, as explained by Virginia Apgar, was to have a tool for quickly assessing newborns who need interventions immediately after delivery and not for the diagnosis of intrapartum hypoxia (41). In addition, different countries have used different cut-off points for abnormal Apgar score. For example, as part of its diagnostic criteria, the American Academy of Pediatrics defines that an Apgar score <5 is associated with risk of

intrapartum hypoxia and warrants further tests, such as umbilical pH (105). However, morbidity and mortality in infants with a high Apgar score have been reported (106), and our own experience in low-income setting shows that incidences of higher scores in the presence of signs and symptoms of asphyxia are not uncommon. In this regard, 35% of those with a normal (i.e. ≥ 7) Apgar score in our cohort presented with severe hypoxia (low initial oxygen saturation < 80%) on admission to the neonatal unit, indicating that there are challenges during the transition from intrauterine to extra-uterine life at birth, and over-scoring by the midwives. Specifically, several newborns in need of ventilation with early signs and symptoms of encephalopathy were given a normal Apgar score (i.e., Apgar of 10 at 5 minutes) by the midwife. The absence of a proper definition of intrapartum asphyxia, coupled with reliability issues in Apgar scoring, may result in misclassifications (both over- and underestimation) of intrapartum-related neonatal deaths on a global level.

Half of the infants in our cohort, who died of BA and complications of MSAF, died within the first 24 hours. These infants likely progressed to respiratory failure within a short time. We cannot rule out the possibility that the presence of CPAP could have averted some of these early deaths, especially among the newborns who were also premature and particularly vulnerable to early and severe respiratory insufficiency.

Despite the inability to objectively differentiate asphyxia-related deaths from prematurity-related deaths (e.g., blood tests and other measures in

the neonatal unit), we consider that the constellation of clinical findings, including abnormal FHR during labour, lower HR at the initiation of PPV, low HR at the end of PPV, and the need for prolonged PPV, are strongly suggestive that the interrupted placental blood flow is the potential pathway leading to intrapartum-related neonatal deaths (Study II). Furthermore, the delayed HR responses (Study II) observed in newborns who died following PPV in the delivery room were likely a sign of foetal acidaemia and possible myocardial dysfunction due to intrapartum hypoxia/ischemia.

Obviously, there may be cases where both asphyxia and prematurity contributed to mortality, however, prematurity as the primary cause was noted in 15% of neonatal deaths, which is lower than previous reports in Tanzania (2,3). However, our report is based on 7-day mortality and we did not report mortality at 28 days. The pathways to preterm death (as classified in our work) did not appear to involve evidence of intrapartum-related complications, and the delivery room transitions were uneventful in almost all cases. Nevertheless, half of these premature deaths occurred within 24 hours, likely due to immature lungs coupled with the absence of early respiratory support (lack of CPAP or intubation and positive pressure ventilation), as recommended by the WHO (107). Two reasons could possibly explain the lower mortality due to prematurity. First, out-borns were excluded from this study because we would not be able to obtain the complete set of labour and delivery room information that was deemed necessary for this study. Indeed premature newborns constitute half of the newborns who are referred to Haydom Hospital from other

facilities, or from home. Second, based on our presumptive classification of deaths, we cannot rule out a possible overlap of causes of death (e.g., asphyxia versus prematurity) that may have resulted in an underestimation of preterm deaths. For example, premature newborns with signs of asphyxia and in need of ventilation at birth, and thus classified as BA, could have been classified as being related to prematurity, especially in similar rural settings with an inability to monitor labour and the newborn course, including the provision of adequate care. Finally, very few newborns with a GA of less than 34 weeks are born in the hospital, and we suspect that more premature babies are born at home in this rural area, not registered at all, or likely (mis)classified as a fresh stillbirth.

Presumed sepsis was also another major factor for death, contributing to 15% of newborn deaths in this cohort. Our estimates are lower than recent global reports; however, global reports mainly measure 28-day mortality (9,102). Nevertheless, neonatal sepsis remains one of the leading causes of newborn mortality globally, affecting both term and preterm newborns. Preterm newborns are highly susceptible to infections due to their immature immune system, and the majority of newborns who died of presumed sepsis in our cohort were premature; these infants had uneventful delivery room transitions and died after 72 hours. Despite our efforts to classify deaths based on clinical definitions, potential misclassification of deaths likely still exists, especially for late deaths.

The rate of congenital malformation in this report of 11% is consistent with the WHO worldwide estimates, as well as the prior estimates in Tanzania of 14% (6,14). Contrary to our findings, a recent population-based study reported a lower rate of congenital abnormalities <5%; however, this was a community study that also involved newborns who died at home (102). The global reports, which included data from low-income countries, and the current study reflect estimations from facility-based studies, where the majority of complicated pregnancies are likely to deliver. On the other hand, the contribution of congenital abnormalities to specific causes of death is probably significantly underestimated in low- and middle-income setting, because of the limited resources to test and confirm abnormalities. Thus, in the presence of techniques such as chromosomal analysis or microarray, more subtle or specific syndromes could have been diagnosed and would likely have increased the contribution of congenital abnormalities to newborn deaths. Autopsies were not performed in this current study.

To summarise, the assignment of causes of death based on our clinical definitions likely resulted in some misclassification. Based on our definition of BA, prematurity and sepsis, BA may have been overestimated in the absence of umbilical cord pH, and other radiological and laboratory tests. On the other hand, Study II revealed that newborns who were ventilated at birth and subsequently died presented with other signs of asphyxia (abnormal FHR, low newborn HR, and HIE) at birth, supporting our diagnosis of BA.

5.2 Predictors of death and quality of positive pressure ventilation

The findings that tidal volume delivered during the first 60 seconds, and during the whole episode of ventilation, did not increase the risk of death at 7 days, is consistent with prior findings reported in this setting (68). In this report, deaths were recorded up to 7 days, whereas the prior report recorded deaths up to 24 hours. Both newborns who died and survivors received the suggested tidal volumes of around 6 ml/kg, which likely explains the lack of association with subsequent death (Study II). Thus, the results of Study II, together with those of Linde et.al (68), indicate that providers are able to deliver adequate tidal volumes, relying on the chest rise and HR feedback as markers of air entry into the lungs. Notably, this was achieved despite the absence of positive end-expiratory pressure.

Importantly, previous studies carried out in this setting during the implementation of the HBB programme have reported that high mortality after PPV was linked to delays in initiating PPV, i.e., the risk of death and/or admission increased by 12–16% for every 30-second delay in starting PPV (50,108). Time from birth to PPV at Haydom Hospital has remained around 2 minutes (Study II) despite a focus on frequent training sessions during implementation of Safer Births study. Importantly, this delayed time interval includes delayed cord clamping in most cases. During our interview with midwives, improving quality of training sessions was mentioned as an essential step to further improve

time to initiation of PPV (Study III). In our analysis, duration of time to start PPV did not influence outcome (death versus survival), as it was similar in both (Study II).

The findings that an abnormal FHR was associated with a 3-fold increased risk of death reflect the importance of the intrapartum period in determining the outcome of resuscitated newborns. Abnormal FHR detected during labour provides an opportunity to intervene and conduct expedited deliveries where indicated. This was also echoed by the midwives where preparation and good monitoring of labour was thought to increase chances of a newborn to survive (Study III). Indeed, foetal monitoring during labour has been the standard of care worldwide (107). If delivery is not expedited in a timely manner, newborns may be severely depressed at birth, and, as such, they may not respond adequately to PPV with an increase in HR. Low HR <100 bpm at the end of PPV increases the risk of death by 7-fold (Study II). In this context, PPV alone (absence of CPAP or the inability to intubate and ventilate) may not be enough to reverse the pathway to subsequent death.

The delay in achieving a HR of 100 bpm or greater was noted for those newborns who died compared to those who survived (Study II). The slower HR responses to PPV may be related to several factors. First, newborns were likely in secondary apnoea, with profound respiratory and metabolic acidaemia, requiring a prolonged period of ventilation to correct the presumed acidaemia, before an increase in HR was noted (53). Second, the self-inflating bag, without the ability to provide

positive end expiratory pressure (PEEP), likely contributed to delays in establishing FRC, and eventually a slower HR response. Third, the time to achieve the targeted volume of 6 ml/kg, which has been shown to be associated with rapid increase in HR (68), was prolonged in those who died compared to survivors. Difficulties in achieving target volumes might be due to low lung compliance (e.g., in premature newborns) and/or liquid-filled lungs, high mask leak and/or obstructions, and eventually failure to establish FRC. It remains unknown whether HR might have improved more rapidly with adequate inflations, for example, being administered by an experienced provider with avoidance of mask leak and/or obstructed airway, and the use of PEEP.

Moderate and severe hypoxic-ischaemic encephalopathy was also a significant predictor of death among the variables that were recorded during admission. HIE is a major complication following in utero hypoxia/ischemia, and the majority of newborns who suffered an intrapartum-related neonatal death were often likely to present with HIE. Thus, hypoxic-ischaemic encephalopathy remains a critical intermediate pathway to death in infants who suffered intrapartum-related events.

5.3 Factors affecting effective ventilation

Inconsistencies in following the HBB guidelines have been reported previously in this setting (50,75). In Study II, delays in initiating ventilation were noted as PPV was initiated beyond the Golden Minute®. This was often followed by a low ventilation fraction as low as 60% during the first 60 seconds of ventilation, indicating interrupted

ventilation as opposed to the continuous ventilation recommended by the HBB guidelines (Study II). Delays in initiating PPV were reported to occur as a result of the inability to quickly identify those who needed PPV (Study III). Although the clinical signs used to assess newborns immediately after delivery are well known (colour, tone, HR, respirations, and reflexes as indicated in the Apgar score), there still seems to be challenges in assessing a newborn baby correctly, which likely contribute to delays in instituting treatment or interventions. Indeed, identifying those who need PPV is the first and most important step, as, without quick identification, immediate interventions are unlikely. Furthermore, labour monitoring and preparation of resuscitation equipment was mentioned as factors that facilitated the timely initiation of resuscitation (Study III). The fact that labour monitoring was mentioned as a facilitator of ventilation reflects sub-optimal labour monitoring practices, which were also evident in Study II. The monitoring of labour is one of the important steps in ensuring good foetal outcome; therefore, efforts should be geared towards improving and standardising labour monitoring for the benefits of the foetus and the mother.

Fear and anxiety when faced with a baby in need of ventilation was common as was reported in Study III. Fear and anxiety were reported to affect ventilation performance, including the inability to follow the HBB guidelines during resuscitation. Midwives believed that, at times, they are not confident with the progress of the newborn, leading them to stop ventilation and perform other tasks which are not recommended.

Interrupted ventilation was observed in Study II but has also been reported previously in the same setting, reporting an association with 24-hour death when HR decreases to less than 100 bpm during a pause (68,96). Furthermore, interruptions during PPV prolongs recovery as it encourages alveolar de-recruitment during pauses, prolonging the period of time to establishing FRC (109) and hence delays in reversing the hypoxic-ischaemic injury process. Resuscitation is known to be a high-demand stressful situation that normally is accompanied by a certain degree of anxiety that should be well controlled with adequate practice and experience.

Although in our study, newborns received adequate mean tidal volumes, there was significant mask leak of up to 50%, indicating sub-optimal techniques during PPV. In our interviews with the midwives, several factors were mentioned that were perceived to affect techniques and skills. First, the need for further training to enhance skills and coordination during resuscitation was highlighted (Study III). Midwives thought that the training manikin could be improved to incorporate responses that could test the practical skills and knowledge more effectively, coupled with increased frequency of training, as this has been previously reported to improve outcomes (64). Second, fear and anxiety may lead to improper handling of the bag and mask, which could have led to leaks, and, third, a lack of prior assignment of roles before delivery could also influence outcomes, as providers who have more PPV skills maybe focused on other tasks. Despite all the indications of sub-optimal quality of ventilation, PPV was not a predictor of death in our final

model, likely because provision of PPV was quite similar in both groups, but also due to the importance of events that occurred before delivery or during the subsequent postnatal care. Furthermore, due to the programme of continuous resuscitation training offered to providers since the beginning of the Safer Births study, it is possible that the midwives were actually providing larger inflated volumes, and thus maintaining targeted tidal volume despite significant mask leaks (68,76).

5.4 Quality of care in the delivery room and newborn unit

Both Study I and Study II reported moderate hypothermia in almost all admitted newborns. Hypothermia was more common in those who died compared to those who survived. Hypothermia itself has been known to increase the risk of death (34,88) in a dose-dependent manner (33). Additionally, it is known to worsen certain conditions, such as intrapartum asphyxia, apnoea, and respiratory distress (110). Hypothermia may have played a role in increasing further injury to the brain through its effect on the myocardium, resulting in cerebral hypo-perfusion that likely limits response to any PPV provided. The findings relating to hypothermia and the risk it posed to newborns in this study is in contrast to the utilization of controlled therapeutic hypothermia to limit the on-going hypoxic-ischaemic brain injury that is common practice in high-resource settings (111); however this is not yet practical in low-income settings (112). The HBB algorithm instructs the providers to keep the baby warm immediately after birth through drying and

quickly covering the newborn with cloth or blankets to prevent hypothermia. However, in the absence of other thermal control measures, such as a radiant warmer, hypothermia will continue to pose a risk that may not be quantifiable in this setting.

The findings of admission hypoxia (low oxygen saturation) in both Study I and Study II likely reflects the limited ability to provide advanced resuscitation in low-income countries where oxygen saturation monitoring is rarely done, and where CPAP and/or intubation/ventilation is infrequent. Furthermore, international guidelines suggest that oxygen supplementation is not needed during initial resuscitation (56), however, this probably plays a role in those newborns who need prolonged ventilation. On the other hand, without proper monitoring (i.e., pulse oximetry and blenders to titrate oxygen) during care after birth, oxygen can also be deleterious.

The WHO framework for improving maternal and newborn care recognizes quality of care as an important process towards reducing maternal and newborn deaths. Poor quality of care has been shown to mitigate gains in the prevention of maternal, newborn, and child deaths (81). In this study, sub-optimal newborn care was evident during labour and delivery, indicated by the fact that some of the newborns suffering intrapartum-related deaths had either no FHR recorded or their FHR was normal. This was followed by the inability to maintain a consistent

temperature in the normal range, as well as limited laboratory support during postnatal care.

Low-income countries with settings such as Haydom Hospital have a significant opportunity to improve newborn survival through simple strategies, such as thermal control, improved quality of intrapartum monitoring, provision of early CPAP and incorporating laboratory and radiological evaluations into the daily assessment of newborns in the newborn unit. Potential strategies, such as continuous improvement of thermal care, are critically needed, for example, through early skin-to-skin care (114), and the use of overhead heaters or plastic wraps in the delivery room (115) and during the transfer of newborns. To improve the care of small and sick newborns, proven interventions such as CPAP, which is shown to be feasible and effective in low-income settings, are needed (35). The use of antenatal dexamethasone for women at risk of preterm labour or those who have preterm premature rupture of the membranes is still low in low-income countries (116). Antenatal dexamethasone is shown to increase lung maturity and protects against respiratory distress syndrome, but also protects against intraventricular haemorrhage and is a standard practice in the majority of high income countries (29,117). Other long-term strategies to improve the outcomes of pregnancies, such as improved nutrition and improved quality of services delivered during antenatal visits, should go hand-in-hand with the above mentioned strategies.

6 Discussion of the methods

6.1 General consideration

This PhD work took place in the context of a poor rural community with access to only one hospital and several small widely scattered health facilities. Haydom Hospital has conducted multiple research projects and quality improvement initiatives in the maternity ward since 2009 (77). The projects included the pilot HBB programme, which resulted in initiation and implementation of the Safer Births study. Nurses and midwives in the maternity ward have participated in repeated training sessions that may have improved their general skills and knowledge, likely differentiating them from other similar facilities within Tanzania.

This PhD work employed a mixed-methods design. This is a design whereby both qualitative and quantitative methods are used to collect data to answer a specific research question (94). The purpose of using mixed methods was due to complementarity, where the qualitative study complemented the quantitative studies to enhance our understanding of newborn resuscitation from the perspective of the providers; in this case, the midwives.

The research employed a modified sequential explanatory mixed-methods design, which integrated the qualitative and quantitative data during the interpretation of the results (95). The modified explanatory sequential nature of the research required us to conduct the studies in two phases. The first phase comprised the collection and analysis of

quantitative, which generated further questions that were clarified by the qualitative study. Such questions included: what influences you to stop ventilation when the baby has not started breathing on its own? However, during the actual execution of the studies, we conducted analysis at the midpoint of the data collection, and used these findings, together with findings of previous similar study in the same settings, to inform the qualitative study (50,68). The integration of the quantitative and qualitative studies was carried out at the interpretation stage, where the core component was quantitative and the supplemental component was qualitative (118).

The mixed-methods approach helped us to answer our broad aim, which was to identify causes of death and to investigate resuscitation and human factors affecting early newborn outcomes. The qualitative study helped us to better understand what was observed in Study II, as well as in other previous studies that were conducted in the same setting. Inconsistencies in following HBB guidelines, including interrupted ventilations and delays in initiating ventilation, were more clearly understood after interviewing experienced midwives. The demand for team training was evident, as HBB training focuses on single-provider education. In addition to providing answers and a better understanding of the resuscitation and ventilation processes observed in Study II, the qualitative study also provided solutions and a way forward in terms of future resuscitation training as suggested by the midwives. The use of mixed methods provided information that would not be possible to obtain with quantitative studies alone.

However, mixed-method designs come with their own challenges. First, mixed methods require significant resources and time to execute. The quantitative studies were part of the larger Safer Births study, which had already established the infrastructure for data collection. This allowed us to concentrate on the qualitative part of the data collection. Second, the ability to learn and master both qualitative and quantitative studies at the same time is challenging. I invested significant time to learn and understand qualitative methods, including attending qualitative methodology courses. With the help and guidance of my supervisors, I was able to achieve and complete the studies included in this thesis.

The quantitative studies reported here (Studies I and II) were both prospective observational clinical studies, which also have their own methodological strength and challenges, as discussed below.

6.2 Prospective observational studies

Both the quantitative studies in this thesis were observational. This method is known to be an initial step in investigating causal relationships, but observation alone cannot identify causal relationships (119). Indeed they are often hypothesis generating and in some instances serve as a precursor to randomized studies. Prospective descriptive observational clinical studies (Study I and Study II) were undertaken due to our desire to explain the major causes of early neonatal deaths, specifically in this rural setting. We also wanted to determine the quality of PPV in relation to the outcomes of admitted newborns. A description of the population of infants who were delivered and/or ventilated and

were sick enough to be admitted to the neonatal area was completed. The observational nature of these studies allowed us to examine in depth what transpired in the delivery room as well as during the initial hospital stay for a maximum of 7 days.

The goal of any study is to obtain, as accurately as possible, all of the measurements required within the study parameters. However, epidemiological studies are often subject to both random and systematic errors (119). Random error occurs when any difference or variability in the data or measurement cannot be explained. The best way to mitigate random errors is to increase the sample size or to assign study subjects randomly into groups. In Study I, the data collection period was extended to include a large enough number of deaths to allow us to make a meaningful conclusion. In Study II, sample size calculations were based on the time from onset of PPV to HR above 100 bpm. However, during the manuscript reviewing process, the reviewers suggested that we should instead report time from birth to HR above 100 bpm, which we then did. For this variable, the power was lower due to higher variability.

Conversely, systematic errors are not eliminated by increasing sample size. This is because the problem is the system of collecting information or the design of the study. Systematic errors are also referred to as biases. Biases in a study can lead to the underestimation or overestimation of the true relationship that was being studied. Biases also decrease internal validity, defined as the extent to which the answers of the research questions generated by the study are trustworthy and meaningful, based

on the design of the study. Both Studies I and II have potential biases that have to be explained.

Selection bias is a systematic error that stems from the procedures used to select study participants (119). Both Study I and Study II included newborns who were delivered at Haydom Hospital and were admitted to the neonatal area. Because Haydom is a referral hospital, complicated deliveries are more often expected compared to other non-referral facilities. Additionally, the rate of home deliveries around the catchment area is approximately 43%. Anticipated home deliveries usually end up in the hospital if complications arise. The patient population at Haydom is therefore a high-risk population, especially for BA, and has been shown to have actually become increasingly vulnerable from 2014 and onwards, probably because of several patient fees introduced in 2013/2014 (120).

Study II included newborns who were ventilated and admitted thereafter. This is, as expected, a sicker group of newborns. We excluded those who were not ventilated and were able to stay with their mothers because of our interest in the sicker population that was shown previously not to improve with HBB training, specifically, after PPV (50). We also excluded newborns who were not delivered at Haydom Hospital, as we would not be able to obtain a complete set of perinatal characteristics, including ventilation parameters. These excluded newborns might have had different characteristics to those who were included and hence adopting this strategy introduced the possibility of selection bias.

Newborns who died within 30 minutes of delivery were also excluded from both Study I and Study II. We excluded this population because of our initial interest in describing a population of admitted infants. Furthermore, these infants had already been described together with fresh stillborns in a previous publication (39). We could not perform extensive analyses of the outcomes of these newborns. However, it is important to be aware of this exclusion (*n*=17 newborns), especially when reading Paper I, as the reported mortality related to intrapartum events only represents the admitted population and not the entire birth cohort (thus "underestimating" the overall proportion of intrapartum related deaths).

Both Studies I and II have missing information regarding some of the variables, especially clinical information and treatment during admission. Most of the missing information was a result of non-documentation. Because our data collectors were non-clinicians, it was difficult to mitigate this problem. It is likely that incidence of missing information was not completely random, hence resulting in information bias. Missing information appeared more often among those who survived. This may be due to providers not adequately recording information for infants who appeared to be less sick. This implies that the population of newborns who died may have appeared sicker due to the more comprehensive documentation of their vital statistics.

In Study II, ventilation parameters were not available for all newborns who were resuscitated. Approximately 36 ventilation parameters were

missing, in which 4 were for newborns who died within 7 days (Study II). The characteristics of those whose parameters were missing could have been different and hence this introduces the risk of selection bias. We did not perform imputation methods for replacing missing data as they have variable results, especially with clinical data (121).

In Study I, potential causes of death were determined clinically, without laboratory and/or radiological confirmation. This method predisposes the findings to information bias, where errors may arise due to the collection of erroneous data. If the improperly collected information involves categorical variables, it is called misclassification bias. Additionally, gestational age, which was used to define prematurity, was mainly estimated based on the last normal menstrual period. We documented in detail the possible pathways to death, which we believe improved our clinical diagnosis. The assignment of causes of death using clinical signs and symptoms considered a careful constellation of clinical findings, including illustrations with diagrams of possible pathways leading to death (Study I).

In Study II, data were collected by ECG dry-electrode technology. The HR sensor was validated with a regular ECG device (HeartStart MRx, Philips), but this was only performed on adult participants. The newborn resuscitation monitor was also tested in piglets before it was used with humans (122). These procedures helped to improve the NRM, including the ECG, to guarantee accurate measurements of HR and ventilation parameters. The resuscitation monitor was able to detect and record other

parameters, such as pressure during PPV and expired carbon dioxide (CO_2). These parameters (pressure and CO_2) were important during data analyses, as pressure and/or CO_2 curves were used to confirm whether ventilation had occurred when in doubt. However, these parameters were excluded at the beginning, as we thought changes in heart rate, expired tidal volume and other studied parameters were adequate to answer our second research objective. Inclusion of ventilation pressure and expired CO_2 (confirming air entry into the lungs) could have complemented the analyses in Study II.

6.2.1 Confounding factors

A central issue in all observational studies is having little control over possible confounding factors that can create bias and mask cause-and-effect relationships or suggest a correlation where there is none. In their simplest form, confounding factors can be explained as the confusion of effects (119). That is, a certain variable may seem to affect the outcome, when it does not in fact have any causal relationship with the outcome. In Studies I and II, we used logistic regression to control for confounding factors and presented data with adjusted and non-adjusted parameters. Additionally, we performed stratified analysis of term versus preterm newborns (Study I). However, we were not able to control for factors that we could not identify as confounders. Such factors are only resolved by randomization, a strategy which was not possible in this study.

6.2.2 Statistical analysis

We employed non-parametric tests because our data were not normally distributed. The non-parametric tests were employed after testing for normality using the Shapiro-Wilk test. We also performed regression analyses to control for measured confounders. The confidence intervals in most of our analyses are wide, indicating high variability in our data. However, despite the high variability, some of the measures of effect remained quite large. All results that have a *p*-value close to 0.05 should be interpreted with caution. This is because we conducted multiple tests without adjusting the significance level of 0.05 according to the number of tests performed.

6.3 Qualitative study (Study III)

Qualitative studies are considered to be a suitable way to study phenomena that cannot be studied or analysed quantitatively, such as human interactions, human beliefs, and human experiences. This qualitative study has conformed to the accepted criteria for the evaluation of trustworthiness, such as credibility, transferability, confirmability, and dependability, as suggested by Graneheim and Lundman (100).

In order to maintain credibility, that is, how well the data address the research question, we employed several methods. Participants were selected carefully considering their years of service as well as the number of resuscitations that they had previously performed. The inclusion of

only midwives in this study might raise a question about whether involving other cadres might have enriched our results. However, we considered that newborn resuscitation is mainly conducted by the midwives, thus other cadres might have little information as well as little experience or performing newborn resuscitation. In particular, doctors are only present during complicated deliveries and they were not involved with HBB training. We conducted all the interviews using Swahili, a language in which all midwives are fluent, and hence they were able to express themselves freely. The employing of a research assistant to conduct the interviews ensured that midwives were not intimidated about speaking to a doctor or their trainer; instead, they had an outsider who did not work with them on a daily basis. We think that this approach increased the quality of our data, as midwives did not have to face their instructor during the interviews. We used qualitative content analysis, which allowed us to examine the text and make sense of it. We ensured that all relevant data were included in our categories and we presented representative quotations from the transcribed text to illustrate how categories are similar or different. The sorting and labelling of the data was conducted in collaboration between my supervisor and me, ensuring that the interpretations were grounded in the data. Furthermore, the multi-disciplinary team who participated in the analyses comprised a midwife, paediatrician, several obstetricians and an anaesthesiologist, who provided further help in understanding the data, including the context. All of the members of the team were native Swahili speakers except one.

We acknowledge that, during the translation of the transcripts, some information could have been lost due to a lack of proper words in the second language and this may have subsequently altered the meaning of the interview sessions. The risk of a loss of meaning was minimized by placing the English paragraph below the translated Swahili paragraph, and therefore, during analysis it was easy to go back to cross-check the translation with the primary text to confirm the meanings.

Transferability relates to how applicable findings are to other settings or contexts. The detailed description of the study context, selection criteria, and the data collection and analysis process were complemented by quotes to allow readers to judge the applicability of our study in their setting.

Dependability refers to possible change over time in data collection and analysis, and the ability of the researcher to account for the changes. In all individual interviews, the use of an interview guide ensured consistency in terms of the research question and provided openness to new insights through asking open-ended questions. The proposed changes after the pilot interview were discussed and agreed among the research group and the reflections and discussions were noted and used to enrich the analysis and interpretation of the findings. The insights gained were considered in subsequent interviews and during the analysis process. Because we have described our methods in detail, future researchers will be able to repeat our work if they wish to replicate our findings.

Confirmability in qualitative research refers to the degree to which the results of an inquiry could be confirmed or corroborated by other researchers. Our research group comprised midwives, paediatricians, obstetricians, and anaesthesiologists, who brought with them extensive knowledge of newborn resuscitation, which helped to improve the confirmability of our findings. Furthermore, our publications underwent a strict peer review process, which also helped us to improve the presentation of our findings.

6.3.1 Reflexivity and the role of researchers

Researchers working within a qualitative discipline ought to recognize and reflect upon their own pre-understanding of the area of research they are involved in. This is because their pre-understanding will influence the way they conduct, analyse and interpret the study (92). I developed my interest in maternal and newborn health after spending several years working in a newborn unit after completing my residency programme. I was aware of my prior understanding through my background along with my previous work experience, including working as a newborn resuscitation instructor. Reflecting back on these experiences during the preparation of the interview guide, it was easy to predict that "inadequate resuscitation training" would be one main issue raised during the interviews. Inadequate training is a common challenge in Tanzania, and even I experienced this as a problem during my early days of practice. I also noted during the two interviews sessions that I performed that nurses seemed to not want to "open up" to me. This could be due to my

inexperience in conducting interviews, but may have occurred because I had served as an instructor during their training sessions. The use of a neutral research assistant who was not part of the research group likely reduced the effect of this problem. The coding process was completed by first identifying the content area, focusing mainly on the actual text that was generated during interviews. Our pre understanding of issues, such as lack of training, also likely influenced how we dealt with the text, but, because the categories were first generated from the text, our approach to analysis mitigated this problem. While the interpretation of the results was shared among the research group, there is no doubt that my prior understanding may have influenced the analysis and interpretation of the results, as I generated the initial codes, sub-categories and categories. Although there is always some element of interpretation when considering textual data, the process of discussing the understanding emerging from the interview text to identify the latent content with the other members of the research team improved the trustworthiness of the findings.

6.4 Ethical Issues

Medical studies involving human beings are guided by ethical principles that protect and safeguard them as participants. These principles emphasize the values of autonomy, beneficence, non-maleficence and justice, as outlined in the Declaration of Helsinki (123). These ethical principles demand that the researchers carefully consider any predictable risks and burdens to the individuals and groups involved in the research

in comparison with the foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. These considerations were attended to for each of the studies as presented below.

6.4.1 Vulnerable population

It is widely agreed that some research participants are vulnerable. A vulnerable population is defined as a group of individuals who are at a disadvantage or who are incapable of protecting their own interest, and those who may require special care and protection of their welfare and rights (124). The Declaration of Helsinki states that a vulnerable population should be included in a research project only if the research responds to the needs of that group. This PhD project was part of the Safer Births project, which focused on the newborn's transition from intra-uterine to extra-uterine. Pregnant women and their newborns, who are both vulnerable populations according to the above definition, were recruited during their labour and the newborns were followed for 7 days after birth. There was a need to include these vulnerable women and their offspring because we could not study newborn resuscitation in any other population. All precautionary steps were taken to protect the study participants, including obtaining permission from Tanzanian regulatory bodies as well as hospital management. The actual patients that were included likely benefited from the improved training of the healthcare workers in a programme that continued for more than 5 years. The monitoring equipment used in the study included important innovations

that had undergone standard certification in Europe before being approved by the Tanzanian Medical and Drug Authority for use as research equipment. The equipment is now approved and available for universal use, at non-profit prices.

6.4.2 Process for obtaining consent

The observational studies in this PhD did not involve any intervention and posed no risk to participants. The equipment used for data collection did not include any new technology, as both continuous FHR monitoring by Doppler and heart rate monitoring by ECG are existing technologies. As noted earlier, the Safer Births project was an extension of a quality improvement project that started at Haydom Hospital in 2009. As a result, the study obtained permission to continue to collect observational data. However, in addition, permission to have non-medical observers in the labour ward was granted at the beginning of the Safer Births study because of the importance of obtaining timed variables during delivery. All observers were female non-medical staff trained in Good Clinical Practices. All data were de-identified and encrypted for storage and analysis purposes. The Safer Births project had standard operating procedures for data management, processing, sharing, and storage that comply with the new European general data protection regulation (GDPR).

6.4.3 The role of sponsors and funding agencies

The Safer Births project was sponsored by the Research Council of Norway. This PhD project was also funded by the Research Council of Norway through the Laerdal Foundation and Laerdal Global Health. Laerdal Global Health, a not-for-profit company, was responsible for equipment development and production, but all the devices used in the research were designed in close collaboration with clinical staff in Tanzania. The core research team responsible for the planning and execution of the studies was independent of the team of engineers who developed the equipment. However, Laerdal Global Health engineers assisted in interpreting signal data gathered from the newborn resuscitation monitors. Engineers continued to provide technical solutions when there were any equipment malfunctions.

Interventions implemented during labour and delivery have shown to yield maximum gains in terms of newborn deaths averted (41%) followed by care of small and sick newborns (30%). The overall Safer Births project involved multiple studies, including the testing of innovations obtained from Laerdal Global Health aiming to address the burden of perinatal mortality through the improvement of labour and delivery processes. The innovations focused on FHR monitoring and newborn resuscitation, including resuscitation training. The studies included in this PhD project were the only studies to follow-up newborns in the neonatal area for 7 days and to include more clinical parameters, such as admission temperature.

6.5 Strengths, limitations, and generalizability

Our ability to observe all of the deliveries and record ventilation parameters, including duration of time to initiate ventilation and initial HR in the labour ward, and the opportunity to link them to events before delivery was unique. Despite a comprehensive research set-up, the study site/setting was a typical remote rural area with a significant number of newborn deaths. Observations in the labour ward have been ongoing since 2013. While the influence of observers is known to change the behaviour of providers, this influence was likely reduced with such a prolonged study period as ours. We were also able to explore midwives' opinions on resuscitation and link these to what we were observing in the labour ward.

This PhD thesis, like most research studies, has its limitations. The methods for detecting abnormal FHR, i.e., continuous Doppler versus intermittent Pinard stethoscope, was not considered during analyses. The abnormal FHR was based on at least three consecutive auscultations of FHR at different sites for intermittent FHR monitoring and persistent abnormal FHR lasting for at least 3 minutes in continuous monitoring. Midwives were less trained to detect beat variability and abnormal decelerations. Therefore, we did not consider abnormal variability and late decelerations as FHR abnormalities, which increases the potential for false negative FHR abnormalities.

Resuscitations in the labour ward were performed by midwives who were trained in the HBB programme as opposed to a neonatologist or

paediatrician, professionals who would normally be responsible for resuscitations in many high-income countries. Intubation and chest compressions in the delivery room are not part of the HBB algorithm and all newborns were resuscitated with a self-inflating bag without PEEP. Blood gases were not performed, and blood tests and monitoring was minimal. The lack of CPAP and other basic equipment and interventions in the neonatal unit may also represent a limitation. It is our assumption that the outcome of some of the newborns could have been different in the presence of the resources and capacities mentioned above.

The inability to objectively confirm causes of newborn death is another limitation of Study I, despite the efforts to trace the clinical pathways leading to death. Clinical support services, such as radiology and laboratory services, were limited. In Study II, we assumed that expired volume indicated gaseous exchange, which might not always be the case.

Moreover, this thesis was based on an observational hospital-based, single-centre study conducted in a rural setup with fairly limited diagnostic resources. The single-facility nature of the studies does not favour generalizability of the results. However, we believe that the majority of low-income rural facilities are similar to our setting, sharing similar challenges of maternal and newborn care. The generalizability of our results might be possible in such settings. The recording of newborn HR used ECG technology, currently accepted as a method of obtaining a quick HR immediately after birth. The measured HR and ventilation parameters would have been the same for all newborns in other parts of

the world. We recognize the possible sub-optimal care that our women and newborns might have received during labour and delivery. Furthermore, newborn care in our setting is still a challenge and the majority of newborns who died during the course of this research might have survived in other high-resource countries.

7 Conclusions

The findings of this PhD thesis demonstrate the contribution of intrapartum-related neonatal deaths to newborn mortality in this rural sub-Saharan setting. Other causes of 7-day mortality were prematurity, sepsis, and congenital abnormalities.

The data demonstrate the link between intrapartum events, likely through interrupted placental blood flow, to a state of depression at birth, as represented by a low HR at birth, delayed HR responses to PPV, prolonged PPV, and eventually death. Abnormal FHR, HR at the end of ventilation, and duration of PPV were the perinatal predictors of death in this setting. Quality of PPV did not influence the outcomes of resuscitated newborns (survivors versus deaths), likely because there was no difference in tidal volumes received between the two groups. Additionally, hypothermia, hypoxia during admission, and lack of respiratory support such as CPAP likely played a role in increasing mortality.

The findings of this PhD work highlight the potential for basic quality improvement of both intrapartum care through improved foetal monitoring during labour and improvement of care after birth to prevent hypothermia and early respiratory failure. Prioritization of resources to focus on the above mention areas will help to improve survival in the context of limited resources. Providers must become more aware of the danger posed by hypothermia. Furthermore, improved resuscitation

training to build the confidence and capacity of midwives to maximize the provision of PPV is warranted to address their uncertainties and the documented inconsistencies and improve the effectiveness of PPV provision.

7.1 Future studies

The findings that intrapartum-related neonatal deaths predominate as the major presumed cause of death in this rural setting should serve as a catalyst for future studies to determine the actual incidence of intrapartum-related neonatal deaths using standard definitions applied in high-income countries. In addition, foetal-newborn transition needs to be elaborated further, including interventions in the immediate newborn period. Due to a lack of data from low-income settings on morbidity from intrapartum-related hypoxia, studies on how newborns who survive resuscitation continue with their lives through childhood, adolescence and adulthood are also important. Furthermore, a larger, multi-facility qualitative study on factors affecting ventilation in urban areas is important to see whether they do share the same findings with this context. We propose the following studies:

1. Documentation of the foetal-newborn transition, including both normal and abnormal FHR patterns
2. Determination of the incidence of intrapartum-related neonatal deaths using blood gasses and a cut-off point of pH <7.0 immediately after delivery (within 30 minutes)

3. Documentation of effects of continuous focus on effective resuscitation training
4. Implementation of basic interventions in the immediate newborn period and documentation of newborn mortality
5. Determination of the neuro-cognitive outcome of infants/children who have survived resuscitation in low-resource settings
6. A qualitative study exploring providers' opinions regarding newborn resuscitation in urban areas

8 References

1. WHO UNICEF. Levels and trends in child mortality: United Nations Inter-agency Group for Child Mortality Estimation (UN-IGME), 2018 Report. 2018.

2. Afnan-Holmes H, Magoma M, John T, Levira F, Msemo G, Armstrong CE, et al. Tanzania's Countdown to 2015: An analysis of two decades of progress and gaps for reproductive, maternal, newborn, and child health, to inform priorities for post-2015. *Lancet Glob Heal*. 2015;3:e396-409.

3. Tanzania Demographic Health Survery and Malaria Indicator. 2015.

4. United Nations General Assembly. Transforming our world: the 2030 Agenda for Sustainable Development. General Assembley 70 session. 2015.

5. Indicators I-A and EG on M. The Millennium Development Goals Report 2015. United Nations. 2015.

6. World Health Organization. Global Health Observatory (GHO): Data Repository. GHO. 2018. Available from: http://apps.who.int/gho/data/node.home

7. Armstrong CE, Martínez-Álvarez M, Singh NS, John T, Afnan-Holmes H, Grundy C, et al. Subnational variation for care at birth

in Tanzania: Is this explained by place, people, money or drugs? *BMC Public Health*. 2016;16(Suppl 2):795.

8. Armstrong CE, Magoma M, Ronsmans C. Magnitude of maternal and neonatal mortality in Tanzania: A systematic review. *Int J Gynecol Obstet*. 2015;130:98–110.

9. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet*. 2016;388:3027–35.

10. Lawn JE, Blencowe H, Oza S, You D, Lee ACC, Waiswa P, et al. Every newborn: Progress, priorities, and potential beyond survival. *Lancet*. 2014;384(9938):189–205.

11. Lawn JE, Cousens S, Zupan J. 4 Million neonatal deaths: When? Where? Why? *Lancet.* 2005;365:891–900.

12. Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000–2013. *Bull World Health Organ*. 2015;93:19–28.

13. Ersdal HL, Mduma E, Svensen E, Perlman J. Birth Asphyxia: A Major Cause of Early Neonatal Mortality in a Tanzanian Rural Hospital. *Pediatrics*. 2012;129:e1238-1243.

14. Mmbaga BT, Lie RT, Olomi R, Mahande MJ, Kvåle G, Daltveit

AK. Cause-specific neonatal mortality in a neonatal care unit in Northern Tanzania : a registry based cohort study. *BMC Pediatr*. 2012;12:116.

15. Lee ACC, Kozuki N, Blencowe H, Vos T, Bahalim A, Darmstadt GL, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. *Pediatr Res.* 2013;74(suppl 1):50–72.

16. Hiersch L, Krispin E, Aviram A, Wiznitzer A, Yogev Y, Ashwal E. Effect of Meconium-Stained Amniotic Fluid on Perinatal Complications in Low-Risk Pregnancies at Term. *Am J Perinatol*. 2016;33:378–84.

17. Wiswell TE, Henley MA. Intratracheal suctioning, systemic infection, and the meconium aspiration syndrome. *Pediatrics*. 1992;89:203.

18. Addisu D, Asres A, Gedefaw G, Asmer S. Prevalence of meconium stained amniotic fluid and its associated factors among women who gave birth at term in Felege Hiwot comprehensive specialized referral hospital, North West Ethiopia : a facility based cross-sectional study. *BMC Pregnancy Childbirth.* 2018;18:429.

19. Velaphi S, Van Kwawegen A. Meconium aspiration syndrome requiring assisted ventilation: Perspective in a setting with limited resources. *J Perinatol*. 2008;28:S36–42.

20. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold

M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Heal*. 2019;7:e37–46.

21. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Eds CP Howson, MV Kinney, JE Lawn. World Health Organization. Geneva. 2012.

22. Mlay GS, Manji KP. Respiratory distress syndrome among neonates admitted at Muhimbili medical centre, Dar es Salaam, Tanzania. *J Trop Pediatr*. 2000;46:303–7.

23. World Health Organisation. WHO recommendations on interventions to improve preterm birth outcomes [Internet]. 2015. Available from: https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/preterm-birth-guideline/en/

24. World Health Organization. Congenital anomalies [Internet]. 2016. Available from: https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies

25. WHO UNICEF. Every Newborn: An Action Plan To End Preventable Deaths. World Health Organization. 2014.

26. Harvey SA, Blandón YCW, McCaw-Binns A, Sandino I, Urbina L, Rodríguez C, et al. Are skilled birth attendants really skilled? A measurement method, some disturbing results and a potential

way forward. *Bull World Health Organ*. 2007;85:783–90.

27. World Health Organization. Essential newborn care course: trainer's guide [Internet]. World Health Organization. 2010. Available from: http://www.who.int/maternal_child_adolescent/documents/newborncare_course/en/

28. Tanzanian National Guideline for Neonatal Care and Establishment of Neonatal Care Unit. Reproductive and child Health Section; 2019.

29. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2017;(3):CD004454.

30. Massawe A, Kidanto HL, Moshiro R, Majaliwa E, Chacha F, Shayo A, et al. A care bundle including antenatal corticosteroids reduces preterm infant mortality in Tanzania a low resource country. *PLoS One.* 2018;13:e0193146.

31. Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. *Cochrane Database Syst Rev*. 2013;(12):CD001058.

32. Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev*. 2016;(8):CD002771.

33. Laptook AR, Salhab W, Bhaskar B. Admission Temperature of Low Birth Weight Infants: Predictors and Associated Morbidities. *Pediatrics*. 2007;119(3):e643–9.

34. de Siqueira Caldas JP, Ferri WAG, Marba STM, Aragon DC, Guinsburg R, de Almeida MFB, et al. Admission hypothermia, neonatal morbidity, and mortality: evaluation of a multicenter cohort of very low birth weight preterm infants according to relative performance of the center. *Eur J Pediatr*. 2019;178:1023–32.

35. Thukral A, Sankar MJ, Chandrasekaran A, Agarwal R, Paul VK. Efficacy and safety of CPAP in low- and middle-income countries. *J Perinatol.* 2016;36(Suppl 1):S21–8.

36. Carter BS, Haverkamp AD, Merenstein GB. The Definition of Acute Perinatal Asphyxia. *Clin Perinatol.* 1993;20:287–304.

37. Low JA. Intrapartum fetal asphyxia: Definition, diagnosis, and classification. *Am J Obstet Gynecol.* 1997;176:957–9.

38. Sehdev HM, Stamilio DM, Macones GA, Graham E, Morgan MA. Predictive factors for neonatal morbidity in neonates with an umbilical arterial cord pH less than 7.00. *Am J Obstet Gynecol*. 1997;177:1030–4.

39. Ersdal HL, Eilevstjønn J, Linde JE, Yeconia A, Mduma ER, Kidanto H, et al. Fresh stillborn and severely asphyxiated neonates share a common hypoxic-ischemic pathway. I*nt J*

Gynecol Obstet. 2018;141:171–80.

40. Parer J, Livingston E. What is fetal distress? *Am J Obstet Gynecol*. 1990;162:1421–7.

41. Apgar V. A Proposal for a'New Method of Evaluation of the Newborn Infant. *Curr Res Anesth Analg*. 1953;32:250–9.

42. The American College of Obstetricians and Gynecologist. American Academy of Pediatrics. The Apgar Score. *Am Acad Pediatr*. 2015;136(4):1–4.

43. Rooth G, Huch A HR. FIGO News: guidelines for the use of fetal monitoring. *Int J Gynecol Obs*. 1987;25:159–67.

44. National Institute for Health and Care Excellence. Intrapartum care for health healthy women and babies. Nice. 2014.

45. American College of Obstetricians and Gynaecologists. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *Obstet Gynecol*. 2009;114:192–202.

46. Gravett C, Eckert LO, Gravett MG, Dudley DJ, Stringer EM, Mujobu TBM, et al. Non-reassuring fetal status: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine.* 2016;34:6084–92.

47. Ashish AC, Wrammert J, Clark RB, Ewald U, Målqvist M. Inadequate fetal heart rate monitoring and poor use of partogram

associated with intrapartum stillbirth: A case-referent study in Nepal. *BMC Pregnancy Childbirth*. 2016;16:233.

48. Bhutta ZA, Das JK, Bahl R, Lawn JE, Salam RA, Paul VK, et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet*. 2014;384:347–70.

49. Linde JE, Schulz J, Perlman JM, Øymar K, Francis F, Eilevstjønn J, et al. Normal Newborn Heart Rate in the First Five Minutes of Life Assessed by Dry-Electrode Electrocardiography. *Neonatology*. 2016;110(3):231–7.

50. Ersdal HL, Mduma E, Svensen E, Perlman JM. Early initiation of basic resuscitation interventions including face mask ventilation may reduce birth asphyxia related mortality in low-income countries. A prospective descriptive observational study. *Resuscitation*. 2012;83:869–73.

51. Guyton AC, Hall JE. Textbook of Medical Physiology 11ed. Textbook of Medical Physiology. 2006.

52. Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. *J Physiol*. 2013;591:2113–26.

53. Dawes G. Birth Asphyxia, Resuscitation and Brain Damage. Foetal and Neonatal Physiology Year Book. 1968. 141–59 p.

54. Msemo G, Massawe A, Mmbando D, Rusibamayila N, Manji K, Kidanto HL, et al. Newborn Mortality and Fresh Stillbirth Rates in Tanzania After Helping Babies Breathe Training. *Pediatrics.* 2013;131:e353-60.

55. Perlman JM, Risser R. Cardiopulmonary resuscitation in the delivery room. Associated clinical events. *Arch Pediatr Adolesc Med*. 1995;149:20–5.

56. Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2015;132(suppl):204–241.

57. UNICEF. The State of World's Children 2009. United Nations Children's Fund. 2009.

58. Wall SN, Lee ACC, Niermeyer S, English M, Keenan WJ, Carlo W, et al. Neonatal resuscitation in low-resource settings: What, who, and how to overcome challenges to scale up? *Int J Gynecol Obstet*. 2009;107(suppl 1.):S47–64.

59. The American Academy of of Pediatrics. Available from: https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/Helping-Babies-Breathe.aspx

60. Goudar SS, Somannavar MS, Clark R, Lockyer JM, Revankar AP,

Fidler HM, et al. Stillbirth and Newborn Mortality in India After Helping Babies Breathe Training. *Pediatrics*. 2013 Feb;131(2):e344–52.

61. KC A, Wrammert J, Clark RB, Ewald U, Vitrakoti R, Chaudhary P, et al. Reducing Perinatal Mortality in Nepal Using Helping Babies Breathe. *Pediatrics*. 2016;137:e20150117.

62. Ersdal HL, Vossius C, Bayo E, Mduma E, Perlman J, Lippert A, et al. A one-day "Helping Babies Breathe" course improves simulated performance but not clinical management of neonates. *Resuscitation*. 2013;84(10):1422–7.

63. Bang A, Patel A, Bellad R, Gisore P, Goudar SS, Esamai F, et al. Helping Babies Breathe (HBB) training: What happens to knowledge and skills over time? *BMC Pregnancy Childbirth*. 2016 Dec;16(1):364.

64. Mduma E, Ersdal H, Svensen E, Kidanto H, Auestad B, Perlman J. Frequent brief on-site simulation training and reduction in 24-h neonatal mortality-An educational intervention study. *Resuscitation.* 2015;93:1–7.

65. Kamath-Rayne BD, Thukral A, Visick MK, Schoen E, Amick E, Deorari A, et al. Helping Babies Breathe, Second Edition: A Model for Strengthening Educational Programs to Increase Global Newborn Survival. *Glob Heal Sci Pract*. 2018;6:538–51.

66. Schilleman K, Van Der Pot CJM, Hooper SB, Lopriore E, Walther

FJ, Te Pas AB. Evaluating manual inflations and breathing during mask ventilation in preterm infants at birth. *J Pediatr*. 2013;162:457–63.

67. Schmölzer GM, Kamlin OCOF, O'Donnell CPF, Dawson JA, Morley CJ, Davis PG. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. *Arch Dis Child Fetal Neonatal Ed*. 2010;95:F393-7.

68. Linde JE, Schulz J, Perlman JM, Øymar K, Blacy L, Kidanto H, et al. The relation between given volume and heart rate during newborn resuscitation. *Resuscitation*. 2017;117:80–6.

69. Murila F, Obimbo MM, Musoke R. Assessment of knowledge on neonatal resuscitation amongst health care providers in Kenya. *Pan Afr Med J*. 2012;11:78.

70. Conroy N, Kaiwo J, Barr DA, Mitchell L, Morrissey B, Lambert SB. Skills retention 3 months after neonatal resuscitation training in a cohort of healthcare workers in Sierra Leone. *Acta Paediatr Int J Paediatr*. 2015;104:1305–7.

71. Musafili A, Essén B, Baribwira C, Rukundo A, Persson LÅ. Evaluating helping babies breathe: Training for healthcare workers at hospitals in Rwanda. *Acta Paediatr Int J Paediatr*. 2013;102:e34–8.

72. Mildenberger C, Ellis C, Lee K. Neonatal resuscitation training for midwives in Uganda: Strengthening skill and knowledge

retention. *Midwifery*. 2017;50:36–41.

73. Mosley CMJ, Shaw BNJ. A longitudinal cohort study to investigate the retention of knowledge and skills following attendance on the Newborn Life support course. *Arch Dis Child*. 2013;98:582–6.

74. Lindbäck C, K C A, Wrammert J, Vitrakoti R, Ewald U, Målqvist M. Poor adherence to neonatal resuscitation guidelines exposed; an observational study using camera surveillance at a tertiary hospital in Nepal. *BMC Pediatr*. 2014;14:233.

75. Skåre C, Boldingh A-M, Nakstad B, Calisch TE, Niles DE, Nadkarni VM, et al. Ventilation fraction during the first 30s of neonatal resuscitation. *Resuscitation*. 2016;107:25–30.

76. Thallinger M, Ersdal HL, Francis F, Yeconia A, Mduma E, Kidanto H, et al. Born not breathing: A randomised trial comparing two self-inflating bag-masks during newborn resuscitation in Tanzania. *Resuscitation*. 2017;116:66–72.

77. Mduma ER, Ersdal H, Kvaloy JT, Svensen E, Mdoe P, Perlman J, et al. Using statistical process control methods to trace small changes in perinatal mortality after a training program in a low-resource setting. *Int J Qual Heal care*. 2018;30:271–5.

78. Tanzania in figures 2018. Available from: https://www.nbs.go.tz/index.php/en/tanzania-in-figures

79. World Health Organization. The Abuja Declaration. https://www.who.int/healthsystems/publications/abuja_declaration/en/

80. Department of Policy and Planning, Ministry of Health and Social Welfare, United Republic of Tanzania. May 2012. Tanzania National Health Accounts Year 2010 with Sub-Accounts for HIV and AIDS, Malaria, Reproductive, and Child Health. Dar es Salaam, Tanzan.

81. Haws RA, Yakoob M, Soomro T, Menezes E V., Darmstadt GL, Bhutta ZA. Reducing stillbirths: Screening and monitoring during pregnancy and labour. *BMC Pregnancy Childbirth*. 2009;9(suppl 1):S5.

82. Goldenberg RL, McClure EM. Reducing intrapartum stillbirths and intrapartum-related neonatal deaths. *Int J Gynecol Obstet*. 2009;107(suppl):S1–3.

83. United Republic of Tanzania. Health Sector Strategic Plan. 2015. http://www.tzdpg.or.tz/fileadmin/documents/dpg_internal/dpg_working_groups_clusters/cluster_2/health/Key_Sector_Documents/Induction_Pack/Final_HSSP_IV_Vs1.0_260815.pdf

84. United Republic of Tanzania. The National Road Map Strategic Plan to Improve Reproductive, Maternal, Newborn, Child & Adolescent Health in Tanzania (2016 - 2020). One Plan II. 2016. https://www.globalfinancingfacility.org/sites/gff_new/files/Tanz

ania_One_Plan_II.pdf

85. Tunçalp, Were WM, Maclennan C, Oladapo OT, Gülmezoglu AM, Bahl R, et al. Quality of care for pregnant women and newborns - The WHO vision. *BJOG An Int J Obstet Gynaecol*. 2015;122(8):1045–9.

86. World Health Organization. Safer Motherhood: Thermal Protection of the Newborn: A practical guide. 1997.

87. World Health Organization. Essential newborn care. World Health Organization. 2010. Available from: http://www.who.int/maternal_child_adolescent/documents/newborncare_course/en/

88. Mullany LC. Neonatal Hypothermia in Low-Resource Settings. *Semin Perinatol*. 2010;34:426–33.

89. Kiley JP, Eldridge FL, Millhorn DE. The effect of hypothermia on central neural control of respiration. *Respir Physiol*. 1984;58:295–312.

90. Wrammert J, Kc A, Ewald U, Målqvist M. Improved postnatal care is needed to maintain gains in neonatal survival after the implementation of the Helping Babies Breathe initiative. *Acta Paediatr Int J Paediatr*. 2017;106:1280–5.

91. United Republic of Tanzania. 2012 Population and housing census; Population Distribution by Adminstrative Areas. National

Bureau of Statistics. 2013. Available from: http://www.tzdpg.or.tz/fileadmin/documents/dpg_internal/dpg_working_groups_clusters/cluster_2/water/WSDP/Background_information/2012_Census_General_Report.pdf

92. Kruger C, Olsen OE, Mighay E, Ali M. Where do women give birth in rural Tanzania? *Rural Remote Health*. 2011;11:1791.

93. Mdoe PF, Ersdal HL, Mduma ER, Perlman JM, Moshiro R, Wangwe PT, et al. Intermittent fetal heart rate monitoring using a fetoscope or hand held Doppler in rural Tanzania: A randomized controlled trial. *BMC Pregnancy Childbirth.* 2018;18:134.

94. Creswell J, Plano Clark V. Designing and Conducting Mixed Methods Research. SAGE; 2011.

95. Creswell J. Educational Research: Planning, conducting and evaluating quantitative and qualitative research. 4th ed. Pearson Education, Inc.; 2012.

96. Ersdal HL, Eilevstjønn J, Linde JE, Yeconia A, Mduma ER, Kidanto H, et al. Fresh stillborn and severely asphyxiated neonates share a common hypoxic-ischemic pathway. *Int J Gynecol Obstet*. 2018;141:171–80.

97. Köhler BU, Hennig C, Orglmeister R. The principles of software QRS detection. IEEE Engineering in Medicine and Biology Magazine. 2002.

98. Green J, Thorogood N. Qualitative Methods for Health Research. Sage Publications. 2009.

99. Kuzel AJ. Sampling in qualitative inquiry. In: Doing qualitative research. 1992. p. 31–44.

100. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: Concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today*. 2004;24:105–12.

101. Barbour R. Introducing Qualitative Research: a student guide to the craft of doing qualitative research. Sage Publications; 2008.

102. Ahmed I, Ali SM, Amenga-Etego S, Ariff S, Bahl R, Baqui AH, et al. Population-based rates, timing, and causes of maternal deaths, stillbirths, and neonatal deaths in south Asia and sub-Saharan Africa: a multi-country prospective cohort study. *Lancet* Glob Heal. 2018;6:e1297–308.

103. Perlman JM, Risser R. Severe fetal acidemia: Neonatal neurologic features and short-term outcome. Pediatr Neurol. 1993;9:277–82.

104. Rüdiger M, Rozycki HJ. It's Time to Reevaluate the Apgar Score. *JAMA Pediatr*. 2020;174(4):321–2.

105. American Academy of Pediatrics and American Heart Association. Textbook of Neonatal Resuscitation. 6th ed. American Academy of Pediatrics; 2011.

106. Razaz N, Cnattingius S, Joseph KS. Association between Apgar

scores of 7 to 9 and neonatal mortality and morbidity: Population based cohort study of term infants in Sweden. *BMJ*. 2019;365:I1656.

107. WHO Recommendations: intrapartum care for a positive childbirth experience. Geneva: World Health organization; 2018.

108. Ersdal HL, Linde J, Auestad B, Mduma E, Lyanga S, Svensen E, et al. Timing of cord clamping in relation to start of breathing or ventilation among depressed neonates—an observational study. *BJOG*. 2016;123:1370–7.

109. Te Pas AB, Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. *Pediatrics*. 2007;120:322–9.

110. Mathur NB, Krishnamurthy S, Mishra TK. Evaluation of WHO classification of hypothermia in sick extramural neonates as predictor of fatality. *J Trop Pediatr*. 2005;51:341–5.

111. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ*. 2010;340:c363–c363.

112. Pauliah SS, Shankaran S, Wade A, Cady EB, Thayyil S. Therapeutic Hypothermia for Neonatal Encephalopathy in Low- and Middle-Income Countries: A Systematic Review and Meta-

Analysis. *PLoS One*. 2013;8:e58834.

113. Akachi Y, Kruk ME. Quality of care: measuring a neglected driver of improved health. *Bull World Health Organ*. 2017;95:465–72.

114. Mccall EM, Alderdice F, Halliday HL, Vohra S, Johnston L. Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. *Cochrane Database Syst Rev*. 2018;2:CD004210.

115. Leadford AE, Warren JB, Manasyan A, Chomba E, Salas AA, Schelonka R, et al. Plastic Bags for Prevention of Hypothermia in Preterm and Low Birth Weight Infants. *Pediatrics*. 2013;132(1):e128-34.

116. Berrueta M, Hemingway-Foday J, Thorsten VR, Goldenberg RL, Carlo WA, Garces A, et al. Use of antenatal corticosteroids at health facilities and communities in low-and-middle income countries. *Reprod Health*. 2016;13(66).

117. Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes: NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. *JAMA*. 1995;273(5):413–8.

118. Teddlie C, Tashakkori A. Foundations of mixed methods research: Intergrating quantitative and qualitative approaches in the social and behavioural sciences. Sage publications; 2009.

119. Rothman KJ, Greenland S, Associate TLL. Modern Epidemiology, 3rd Edition. The Hastings Center report. 2014.

120. Mduma E, Kvaløy JT, Soreide E, Svensen E, Mdoe P, Perlman J, et al. Frequent refresher training on newborn resuscitation and potential impact on perinatal outcome over time in a rural Tanzanian hospital: an observational study. *BMJ Open*. 2019;9:e030572.

121. Gorelick MH. Bias arising from missing data in predictive models. *J Clin Epidemiol*. 2006;59:1115–23.

122. Linde JE, Eilevstjønn J, Øymar K, Ersdal HL. Feasibility of a prototype newborn resuscitation monitor to study transition at birth, measuring heart rate and ventilator parameters, an animal experimental study. *BMC Res Notes*. 2017;10:235.

123. World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2194–2194.

124. Liamputtong P. Researching the Vulnerable. Researching the Vulnerable. A guide to sensitive research methods. Sage Publications; 2011.

Appendices

Appendix 1 – ***Safer Births Data Collection Form***

Study Station	☐1 MNH ☐ 2 HLH
Mother Hospital ID (HLH) or **Case note number (MNH)**	☐☐☐☐☐☐☐☐☐☐
Newborn ID (HLH) or **Delivery Number (MNH)**	☐☐☐☐☐☐☐☐☐☐
***If Multiplies (twins and more)**	☐ Newborn number (write 8 if single birth)
Date of birth	☐☐ DAY ☐☐ MONTH ☐☐ YEAR
Time of birth	☐☐ HOURS ☐☐ MINUTES
Antenatal care attendance	☐1 YES ☐2 NO
Antenatal problem	☐1 YES ☐2 NO
Source of admission	☐1 Referral: _____ ☐2 Home 3☐Maternity home (waiting area) ☐☐:☐☐ Hours since start of labour
DURING ADMISSION	Date: ☐☐ ☐☐ ☐☐ (ddmmyy)Time ☐☐:☐☐
***Gestational age**	☐1 Term ☐2 Pre-term ☐☐ WEEKS
***Foetal Heart Rate (FHR) on admission**	☐1 Normal (120-160 BPM) ☐2 Abnormal; Confirmed Doppler ☐1YES ☐2NO ☐3 Not detectable ☐9 Not measured
***Cervical dilatation (on admission)**	☐☐ CM ☐9 Not measured
***Presentation**	☐1 Cephalic ☐2 Breech ☐ 3 Others_____
***CONSENT**	☐1 YES ☐2 NO

	☐3 NA *(If NO or NA skip to Labour information)*
SCREENING (all with * mark) **Eligible if:**	**Singleton (Y)** **Gestation age (term)** **Cephalic presentation (Y)** **FHR (120-160 BPM)** **Cervical dilatation (≤7cm)** **Placenta abruption/praevia (N)** **Ruptured uterus (N) Consent (Y)**
ELIGIBLE for FHR study?	☐1 YES ☐2 NO *(If NO skip to Labour information)*
RANDOMISATION	☐1 Pinard fetoscope ☐2 Handheld Doppler ☐3 Laerdal FHR monitor; number of monitor ☐☐
LABOUR/DELIVERY INFORMATION	
Maternal fever	☐1 YES ☐2 NO
Maternal Infection (more than 1 is possible)	☐1 NO ☐2 uterine ☐3 malaria ☐4 HIV ☐5 Others; mention _____
Equipment checked	☐1 YES ☐2 NO ☐3 NA (MNH)
Delivery kit present	☐1 YES ☐2 NO ☐3 NA (MNH)
Resuscitation kit present	☐1 YES ☐2 NO ☐3 NA (MNH)
Bag mask present	☐1YES ☐2 NO ☐3 NA (MNH)
Fetal heart rate (every 30 minutes in 1. Stage and every 15 minutes in 2. Stage)	☐1 Normal (120-160 BPM) ☐2 Abnormal: Time ☐☐:☐☐ ☐3 Not detectable ☐9 Not measured
Device mostly used for taking FHR	☐1Pinard fetoscope☐2 Handheld Doppler ☐3 None
If abnormal; what rate **Confirmed with handheld Doppler**	☐☐☐ BPM *(if with Doppler skip next question)* ☐1 YES ☐2 NO ☐☐☐ BPM

Duration of labour	
1st. stage **2nd. stage** **3rd. stage**	☐☐:☐☐ hrs:min ☐☐:☐☐ hrs:min ☐☐:☐☐ hrs:min
Last FHR measurement before delivery	☐☐☐ BPM; Time ☐☐:☐☐ Confirmed Doppler ☐1 YES ☐2 NO ☐ Not measured
Amniotic Fluid colour	☐ 1 Clear ☐ 2 Slight Meconium ☐ 3 Thick Meconium ☐ 4 Blood stained
Mode of delivery *(If 1,3,4 or 5 skip to HCW attending delivery)*	☐1 SVD ☐2 CS ☐3 ABD ☐4 Vacuum ☐5 Others; mention _____
Category of CS	☐1 Emergency CS ☐ 2 Elective CS
If CS; what indication	☐ 1 Obstructed labour ☐ 2 Fetal distress ☐ 3 Previous CS ☐ 4 Malpresentation ☐ 5 Others; mention_____
HCW attending the delivery	☐ 1 Midwife ☐ 2 Ward attendant ☐ 5 Doctor ☐3 Student ☐ 4 Clinical officer ☐ 6 None
LABOUR COMPLICATION	
Obstructed labour	☐1 YES ☐2 NO
***Uterine Rupture**	☐1 YES ☐2 NO
Pre-eclampsia **Eclampsia**	☐1 YES ☐2 NO ☐1 YES ☐2 NO
Cord prolapse	☐1 YES ☐2 NO
***Bleeding (i.e. placenta previa etc)**	☐1 YES ☐2 NO
Shoulder dystocia	☐1 YES ☐2 NO

NEONATAL INFORMATION	
Birth weight	☐☐☐☐ GRAM
Sex of newborn	☐1 MALE ☐2 FEMALE ☐ 3 Ambiguous
Time intervals (for HLH)	
birth – breathing	☐☐☐☐ SEC *(skip if resuscitation is needed)*
birth - cord clump	☐☐☐ SEC
birth - use of heart rate buckle	☐☐☐ SEC *(skip if not used)*
	Name of NRM monitor _____
Apgar score (range 0-10)	☐☐ 1 MIN ☐☐ 5 MIN
RESUSCITATION ATTEMPTED	☐1 YES; Fill in this section ☐2 NO; *go to next section*
Use of Newborn Resuscitation Monitor (NRM)	☐1 YES ☐2 NO ☐3 NA
	If Yes; name of monitor _____
	If No; mention reason _____
Stimulation	☐1 YES ☐2 NO
Suction	☐1 YES; Penguin ☐2 YES; not Penguin ☐3NO
Bag mask ventilation	☐1 YES ☐2 NO
Time intervals (for HLH)	
birth - breathing or ventilation	☐☐☐☐ SEC ☐1 Breathing ☐2 Ventilation
ventilation - breathing or death	☐☐☐☐☐☐SEC ☐1 Breathing ☐2 Death
	☐3 Mechanical ventilation
Did the attending HCW/midwife call for help to resuscitate?	☐ 1 YES ☐ 2 NO
Who provided resuscitation	☐1 Midwife ☐ 2 Operating Nurse
	☐3 Clinical Officer ☐4 Doctor
	☐5 Other; _____ ☐6 AMO

Last HBB full course attended?	☐☐ MONTH ☐☐ YEAR ☐ 2 NA
PERINATAL OUTCOME **within 30 min**	☐1 NORMAL ☐2 Admitted neonatal unit (room 20 in HLH or 36 in MNH) ☐3 Death (END) ☐4 Stillbirth (fresh) ☐5 Stillbirth (macerated) *(If 3,4, or 5 skip neonatal outcome)*
Neonatal outcome at 24 hours postpartum /or at discharge **_____ hours postpartum**	☐1 NORMAL ☐2 Still in neonatal unit ☐3 Death ☐6 Seizures
Neonatal outcome of admitted baby at _____ days (max 7 days)	☐1 NORMAL ☐2 Still in neonatal unit ☐3 Death ☐6 Seizures

Observer's initials _____

Appendix 2 – ***Neonatal Room Data Collection Form***

Date of admission to Room 20	DAY ☐☐ MONTH ☐☐ YEAR
Time of admission	☐☐ HOURS ☐☐ MINUTES
Id no of Mother	☐☐☐☐☐☐☐☐☐☐
Parity **Village**	☐☐ _____
Sex of child **Birth weight**	☐1 MALE ☐2 FEMALE ☐☐☐☐ GRAM
Place of delivery	☐1 Home ☐2 HLH ☐3 Other facility
Reason for admission to neonatal unit	☐1 PREMATURE ☐2 DIFFICULT IN BREATHING ☐3 FEVER ☐4 CONGENITAL ABNORMALITIES ☐5 MULTIORGAN FAILURE ☐6 SEIZURES ☐7 OTHER _____
Admission parameters **Temperature** **Pulse** **O_2 Saturation** **Blood glucose**	 ☐☐.☐◦c ☐☐☐ beats/min ☐☐☐ % ☐☐.☐mmol
Hypoxic Ischaemic Encephalopathy score	Day 1 ☐☐ Day 2 ☐☐ Day 3 ☐☐ Day 4 ☐☐ Day 5 ☐☐ Day 6 ☐☐ Day 7 ☐☐
Seizures within first 7 days	☐ None ☐ < 3 times a day ☐ > 3 times a day

Discharged HOME	☐☐ Day ☐☐ Month ☐☐ Year ☐☐ Hrs ☐☐ Min
Discharged to POSTNATAL	☐☐ Day ☐☐ Month ☐☐ Year ☐☐ Hrs ☐☐ Min
Discharged to KMC room	☐☐ Day ☐☐ Month ☐☐ Year ☐☐ Hrs ☐☐ Min
Date and time of DEATH	☐☐ Day ☐☐ Month ☐☐ Year ☐☐ Hrs ☐☐ Min
Still admitted after 7days	☐1 Yes ☐2 No
Duration of hospital stay	_____
Discharge Diagnosis	1. _____ 2. _____
Cause of death **a. Immediate cause of death** **b. Underlying cause of death**	_____ _____

Observer's initials _____

Appendix 3 – ***Interview Guide***

General questions

1. Tell me about your experience of resuscitating a non-breathing baby
2. Tell me about your best/worst experience during resuscitation…
    a. What do you think helped you to overcome the situation/or what made the situation worse?
    b. What do you think has to be done to help midwives cope with such situations
    c. What did you learn from the two scenarios that you have just explained?
3. How confident/comfortable are you ventilating a non-breathing baby?
    a. What makes you confident/comfortable during ventilation
    b. What about the rest of the midwives?
4. In what way does stress and/or anxiety affect you/midwives during resuscitation?
    a. If positive/negative effect should elaborate more

Initiating ventilation

1. What makes you decide to start ventilation instead of continue with stimulation/suction if the baby has not yet started breathing?

2. What makes you decide to continue with stimulation/suction instead of starting ventilation if the baby has not yet started breathing?
    a. What makes you delay starting ventilation
    b. What makes you to start ventilation immediately

Continuation of Ventilation

1. What makes you stop ventilation when baby has not started breathing on its own?

Communication/cooperation

1. How would you describe collaboration/cooperation/teamwork between midwives during resuscitation of non-breathing baby?
    a. If there is more than on midwife on resuscitation table, how do you organise yourselves during the resuscitation
2. How would you describe trust/belief between midwives when it comes to resuscitating a non-breathing baby?
3. How can you describe the attitude of the midwives in the labour ward?
    a. How does this effect resuscitation of newborns?

Training

1. How did resuscitation training influence your work as a midwife

2. Can you describe the difference between resuscitation training that you have attended and actual resuscitation that you have performed on a newborn?
3. Do you think the training should be conducted differently? How?

Resuscitation protocol

1. What is your opinion regarding the HBB guidelines that is currently in use?
2. How easy or difficult is it to follow them?
3. How often do you think the guidelines are being followed during resuscitation? and why?
4. If the guideline is not followed more often, what could be the reasons?

Laerdal Newborn Resuscitation Monitor (LNRM)

1. Tell me about your experience of using LNRM
2. Can you tell me how does this device influence/effect the way you perform resuscitation
3. What are the advantages/disadvantages of having this device around you during resuscitation

In what way do you think this device should be improved for future use?

Paper I

PLOS ONE

RESEARCH ARTICLE

Potential causes of early death among admitted newborns in a rural Tanzanian hospital

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Abstract

Background

Approximately 40,000 newborns die each year in Tanzania. Regional differences in outcome are common. Reviewing current local data, as well as defining potential causal pathways leading to death are urgently needed, before targeted interventions can be implemented

Objective

To describe the clinical characteristics and potential causal pathways contributing to newborn death and determine the presumed causes of newborn mortality within seven days, in a rural hospital setting.

Methods

Prospective observational study of admitted newborns born October 2014–July 2017. Information about labour/delivery and newborn management/care were recorded on data collection forms. Causes of deaths were predominantly based on clinical diagnosis.

Results

671 were admitted to a neonatal area. Reasons included prematurity n = 213 (32%), respiratory issues n = 209 (31%), meconium stained amniotic fluid with respiratory issues n = 115 (17%) and observation for < 24 hours n = 97 (14%). Death occurred in 124 infants. Presumed causes were birth asphyxia (BA) n = 59 (48%), prematurity n = 19 (15%), presumed sepsis n = 19 (15%), meconium aspiration syndrome (MAS) n = 13 (10%) and congenital abnormalities n = 14 (11%). More newborns who died versus survivors had oxygen saturation <60% on admission (37/113 vs 32/258; $p \leq 0.001$) respectively. Moderate hypothermia

Competing interests: The authors have declared that no competing interests exist.

on admission was common i.e. deaths 35.1 (34.6–36.0) vs survivors 35.5 (35.0–36.0)˚C ($p \leq 0.001$). Term newborns who died versus survivors were fourfold more likely to have received positive pressure ventilation after birth i.e. 4.57 (1.22–17.03) ($p<0.02$).

Conclusion

Intrapartum-related complications (BA, MAS), prematurity, and presumed sepsis were the leading causes of death. Intrapartum hypoxia, prematurity and attendant complications and presumed sepsis, are major pathways leading to death. Severe hypoxia and hypothermia upon admission are additional contributing factors. Strategies to identify fetuses at risk during labour e.g. improved fetal heart rate monitoring, coupled with timely interventions, and implementation of WHO interventions for preterm newborns, may reduce mortality in this low resource setting.

Introduction

In Tanzania, approximately 40,000 newborns die annually due to three major causes; birth asphyxia (BA), prematurity and presumed infections [1,2]. Approximately half of newborn deaths occur within the first 24 hours, and two thirds by the seventh day [3]. Early newborn deaths result mainly from intrapartum complications and immediate postnatal problems including apnea, meconium and hypothermia, which may be prevented or ameliorated by timely interventions.

BA defined as a 5-minute Apgar score <7 and lack of spontaneous respirations after birth, accounts for approximately 0.7 million global deaths [4]. Specifically, in Tanzania, BA accounts for 27 to 45 percent of neonatal deaths; this range in BA reflects regional differences in the country [2, 5, 6]. Globally, prematurity and its attendant complications is the leading cause of neonatal mortality [5]. In Tanzania, approximately 11 percent of newborns are born premature i.e. <37 weeks but they account for 23–35 percent of newborn deaths [1,2]. While in many resource-replete countries, the lower limit of viability approximates 24 weeks of gestation [7], low-resource countries still struggle to prevent premature deaths even at 28 weeks [8]. Recently, the WHO recommended several interventions including administration of antenatal corticosteroids to women at imminent risk of premature labour, and early initiation of continuous positive airway pressure (CPAP) for newborns with respiratory distress syndrome (RDS), geared towards reducing preterm mortality in low-resource settings [9]. A third leading cause of death are infections, which contribute to anywhere from 10 to 30 percent of newborn mortality in Tanzania [1, 2]. However, the diagnosis of infection is often presumed because blood cultures and other ancillary tool are not consistently obtained. Prior to implementation of any potential intervention current local data are needed, with a specific focus on potential causal pathways leading to mortality, in order to facilitate targeted specific interventions. The objectives of this study were to: (1) determine the presumed causes of newborn mortality in a rural hospital setting, and (2) describe the clinical characteristics and potential causal pathways contributing to newborn death within seven days.

Materials and methods

From October 2014 to July 2017, a prospective observational study was conducted at Haydom, a rural hospital in Northern Tanzania, of consecutively admitted newborns followed until

discharge or death within the first seven days. Ethical approval was granted by the National Institute for Medical Research in Tanzania (Ref. NIMR/HQ/R.8a/Vol.IX/1434) and the Regional Committee for Medical and Health Research Ethics in Norway (Ref.2013/110). Informed consent was not required by the ethical committees because the study was descriptive.

HLH has approximately 4500 deliveries annually, which is about 53% of deliveries in the catchment area. Less than 10% give birth in other facilities and the remainder gives birth at home. The hospital provides emergency obstetric services 24 hours a day with a caesarean section rate of 22% [10]. Deliveries and newborn resuscitations were mainly conducted by 18–22 midwives with three shifts. Midwives were trained in Helping Babies Breathe [11] and short ventilation training sessions were conducted on a weekly basis with full HBB refresher training twice yearly. The management of newborns born through meconium stained amniotic fluid (MSAF) focused on clearing the oro-pharynx with a bulb suction, when meconium was present, followed by positive pressure ventilation for the non-breathing infant.

The hospital's newborn area accommodates 10–15 newborns with one general practitioner in charge of the neonatal ward, supervising intern doctors. Admission criteria include prematurity, 5-minute Apgar score <7, fever (temperature >38˚C), signs of respiratory compromise, i.e. intercostal, subcostal retractions or grunting and infants with congenital abnormalities. Premature newborns are nursed under shared radiant warmer and term newborns are nursed in locally made 'baby cots'. Interventions include intravenous fluids, intravenous antibiotics, oxygen therapy using oxygen concentrators, and phototherapy, as clinically indicated. Stable newborns are allowed to breastfeed, if not, mothers express milk and it is administered either via an oro-gastric tube or via a cup. Stable premature newborns of <1800 grams are nursed skin to skin until they attain a minimum discharge weight of 1800 grams. Provisional diagnoses and presumed causes of death were assigned by the attending doctor during the ward round.

Trained research assistants (n = 14) observed and recorded every delivery in the labour ward and theatre on a data collection form. This form contained antenatal and perinatal information. Information related to admitted newborns was captured using a second data collection form. Inclusion criteria were all newborns delivered at HLH and were alive at the time of admission to the newborn area. Exclusion criteria included: all newborns delivered outside HLH, and newborns who died in the delivery room within 30 minutes of birth. Newborns who died in the delivery room were excluded as they have been reported previously [12]. More specific definitions are noted in Table 1.

Initial management of admitted newborns

Management of newborns followed the principles outlined in the WHO Essential Newborn Care guidelines which included routine administration of intramuscular Vitamin K injection (1 mg stat for term and 0.5 mg for preterm) to all admitted newborns [13]. Axillary temperature and blood glucose measurements were obtained using a digital thermometer and commercial glucometer, respectively, within 30 minutes of admission. Hypoglycemia, defined as blood glucose below 2.5 mmol/L [14], was treated with intravenous bolus 3 mls/kg 10% dextrose followed by feeding or maintenance with 10% dextrose. Seizures were treated with intravenous phenobarbital at a loading dose of 20 mg/kg, followed by maintenance dose of 5 mg/kg/day. Newborns with history of BA were categorized clinically as either mild, moderate and severe hypoxic ischaemic encephalopathy using the Thompson scoring system [15]. Antibiotics (ampicillin 50 mg/kg/day and gentamycin 4 mg/kg/day) were given to at risk newborns, i.e. premature newborns, infants with presumed MAS and/or BA, for at least 48 hours because of

Table 1. Specific definitions used to define conditions.

	Definition
Gestational age	Self-report of the last normal menstrual period and distance measured from symphysis pubis to the fundus
Prematurity	Gestational age <37 weeks
Low birth weight	Birth weight <2500 grams.
Presumed Neonatal sepsis	One or more clinical signs of bacterial infection: pallor, poor perfusion, bradycardia, apnea, tachypnea (>60 breaths/minute), dyspnoea (grunting, nasal flaring, retractions), temperature instability (≥38˚C or <36˚C), difficulty feeding and distended abdomen.
Pneumonia	Difficulty in breathing, tachypnea (respiratory rate >60 breaths/minute) without history of birth asphyxia.
Birth asphyxia	1) Failure to initiate spontaneous breathing and/or 5-minute Apgar score <7 in addition to clinical evidence of encephalopathy. 2) Gestational age <32 weeks with a history of suspected intrapartum related hypoxia (abnormal fetal heart rate, labour complications, no respiratory efforts or the need for positive pressure ventilation)
Respiratory distress syndrome	Considered in a preterm baby with chest retractions within two hours after delivery with exacerbation over the first 24–48 hours of life, followed by a stable phase till 72 hours, then improvement between the 3rd and 6th day.
Meconium aspiration syndrome	Onset of respiratory distress immediately after birth or few hours, with history of meconium stained amniotic fluid, meconium around the oro-pharynx or meconium stained skin.
Meconium stained amniotic fluid	Amniotic fluid stained with thick meconium
Hypoxic-ischaemic encephalopathy	Clinical diagnosis characterized as mild, moderate and severe using the Thompson scoring system

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the inability to exclude infections. If sepsis was suspected based on clinical signs [16, 17], the antibiotics were changed to ceftriaxone 50 mg/kg/day for 10 days. Continuous positive airway pressure (CPAP) and intubation was not available to assist infants with respiratory difficulty. Radiological investigations such as chest x-rays and cranial ultrasounds were infrequently obtained because of difficulties transporting unstable newborns to the radiology department. Blood cultures, full blood counts and C-reactive protein measurements were rarely available.

Data analysis. The Chi-square or Fisher exact test was used to test for differences between categorical variables, as appropriate. The Mann-Whitney U test was used to test for differences between groups for continuous variables when test for normality showed that the data where not normally distributed. Logistic regression was used for modelling the impact of risk factors for death among admitted newborns. First a stepwise backward selection method with the retention of predictors with $p<0.05$ was used, and afterwards excluded variables were re-entered one by one and kept if found significant. The results are presented as Odds Ratio (OR) with 95% confidence intervals (CIs). Variables obtained on initial assessment during admission were not used because of missing data. Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, N.Y. USA).

Results

During the study period, there were 10629 deliveries, 10320 were live newborns of birth weight 3311±529 grams and GA 38.8±1.8 weeks, 309 were stillborn and 26 newborns died within 30 minutes (the latter newborns died from BA) [12]. Of the remaining 10294 newborns, 9623 were normal and stayed with the mother, and 671 were admitted to the neonatal area (Fig 1). Of the admitted newborns, a total of 124/671 (18%) died within seven days; of these 61 (49%) within 24 hours, an additional 38 (31%) within 72 hours and 25 beyond 72 hours of life.

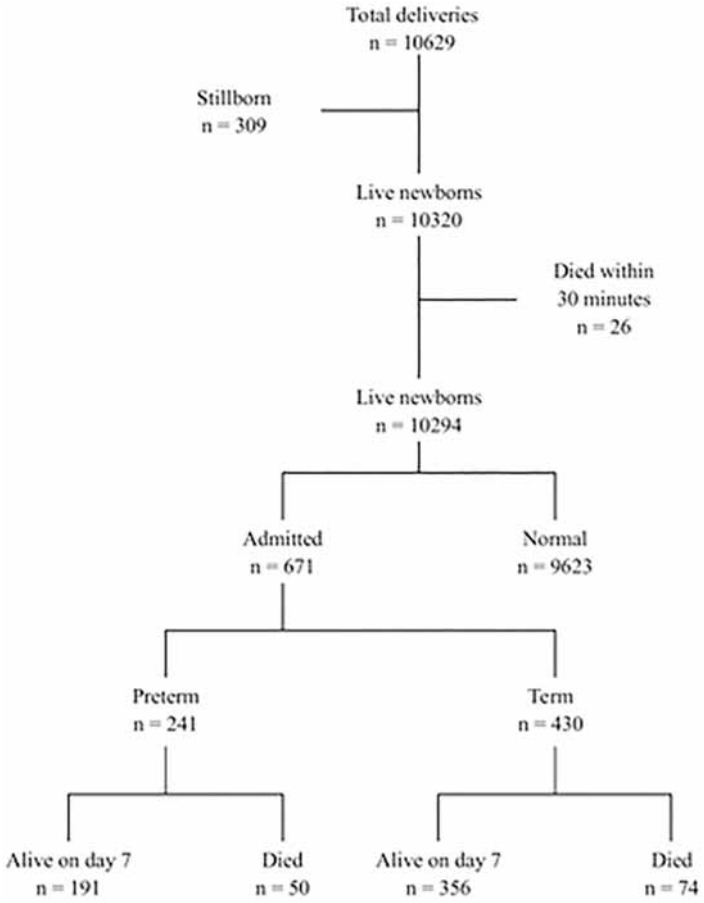

Fig 1. Flow diagram of newborn delivered and outcome after 7 days.

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Delivery room management (n = 10320)

At delivery 2785/10320 (27%) were stabilized with stimulation and/or suctioning and 691 (6.7%) of these newborns were ventilated immediately after delivery. MSAF was present in 2561 (25%) of all live newborns.

Characteristics of admitted newborns (n = 671)

Of the 671 admissions, 241 (36%) were premature and 297 (44%) were of low birth weight. A total of 314 (46%) of the admitted newborns were ventilated in the delivery room; of these 17% were premature. Reasons for admission included complications of prematurity *n* = 213 (32%), respiratory issues *n* = 209 (31%), MSAF with respiratory issues *n* = 115 (17%), infants admitted for observation <24 hour (e.g. post-caesarean section, infants with weight above 3.8 kg) *n* = 97 (14%), and other indication 37 (5%).

Presumed causes of death (*n* = 124)

The presumed causes of death included BA (n = 59), complications related to MSAF (*n* = 13), prematurity (*n* = 19), presumed/suspect infection (*n* = 19) and secondary to complication related to congenital anomalies (*n* = 14). Each is briefly reviewed below:

1. BA (*n* = 59) (47%) was the leading cause of death which included 11 (22%) premature newborns (Fig 2). Labour was complicated by an abnormal fetal heart rate in 13 (22%) cases. In 7(12%) the foetal heart rate was not measured. Delivery was via emergency caesarean section in 30 (51%) cases and in 34 (58%) there was associated MSAF (Fig 2). Positive pressure ventilation was applied in the delivery room in 54 (92%) newly borns. Upon admission to the neonatal ward, moderate hypothermia (temperature 32–36˚C) was noted in 40 (69%) and moderate to severe hypoxia (saturation <80%) in 28 (58%) newborns (Fig 2). Hypoxic-ischemic encephalopathy (HIE) developed in 28 (48%) newborns, was severe in 17 (29%) and moderate in 11 (19%) of these newborns. Seizures were noted in 16 (27%) newborns. Death occurred within 24 hours in 35 (60%), and between 24 and 72 hours in 16 (33%) newborns.

2. MSAF was present in 254/671 (38%) of newborns; 122 (48%) cases were categorized as thick. There were 51 (20%) newborns with MSAF who died including 34 (13%) with BA (see above), 4 newborns with presumed/suspect sepsis and 13 (5%) additional newborns who died secondary to presumed MAS (Fig 3). For the latter newborns, the fetal heart rate during labour was normal in 12 (92%) cases. The MSAF was categorized as thick (n = 9) (69%) and delivery was via emergency CS in 9 (69%) cases. Positive pressure ventilation was applied in 9 (69%) and the 5-minute Apgar score was > 7 in all 13 newly borns. Moderate hypothermia was noted in 8/13 (61%) and moderate to severe hypoxia in 8 (61%) newborns. Death occurred within 24 hours in 7 (54%) and between 24 and 72 hours in 5 (38%) newborns.

3. Prematurity and its attendant complications contributed to 19 (15%) of all newborn deaths. Upon admission, all 19 had a normal foetal heart rate and the heart rate continued to be normal during labour in 17/19 cases; in 2 cases the foetal was not measured (Fig 4). Delivery was vaginal in 14 (74%) and via emergent caesarean section in 4 (21%) newborns. No newborn received positive pressure ventilation in the delivery room. Moderate to severe hypothermia was noted in 14 (74%) and moderate to severe hypoxia in 7 (37%) newborns. Complications of prematurity that led to death included respiratory distress syndrome (*n* = 11) (including 8 who died within 72 hours), recurrent apnoea (*n* = 2), necrotizing enterocolitis (*n* = 1), haemorrhage due to presumed Vitamin K deficiency (*n* = 1) and two newborns admitted with severe hypothermia (temperature <32˚C). Death occurred within 24 hours in 11 (58%), between 24 and 72 hours in 3 (16%) and beyond 72 hours in 5 (26%) newborns.

4. Presumed/ suspect sepsis contributed to 19 (15%) deaths; 16 (84%) were premature. The foetal was normal in 15 (94%) neonates; in 3 cases the heart rate was not measured (Fig 5). Positive pressure ventilation was applied in 5 (26%) newly borns and in all cases the 5-minute Apgar score was ≥7. Moderate to severe hypothermia was noted in 12 (63%) and moderate to severe hypoxia in 11 (58%) newborns. Three of the newborns had presumed pneumonia. Death occurred within 24 hours in 1 (5%), between 24 and 72 hours in 4 (21%) and beyond 72 hours in 14 (74%) newborns.

5. Congenital abnormalities (*n* = 14) were associated with early deaths. These included presumed congenital heart disease (*n* = 3), anencephaly (*n* = 1), gastroschisis (*n* = 1), presumed congenital Rubella syndrome (*n* = 1), trachea-oesophageal fistula (*n* = 1), prune belly syndrome (*n* = 1), Hydrops fetalis (*n* = 1) and Down syndrome (*n* = 1). Four newborns had dysmorphic features which could not be linked to a definitive syndrome.

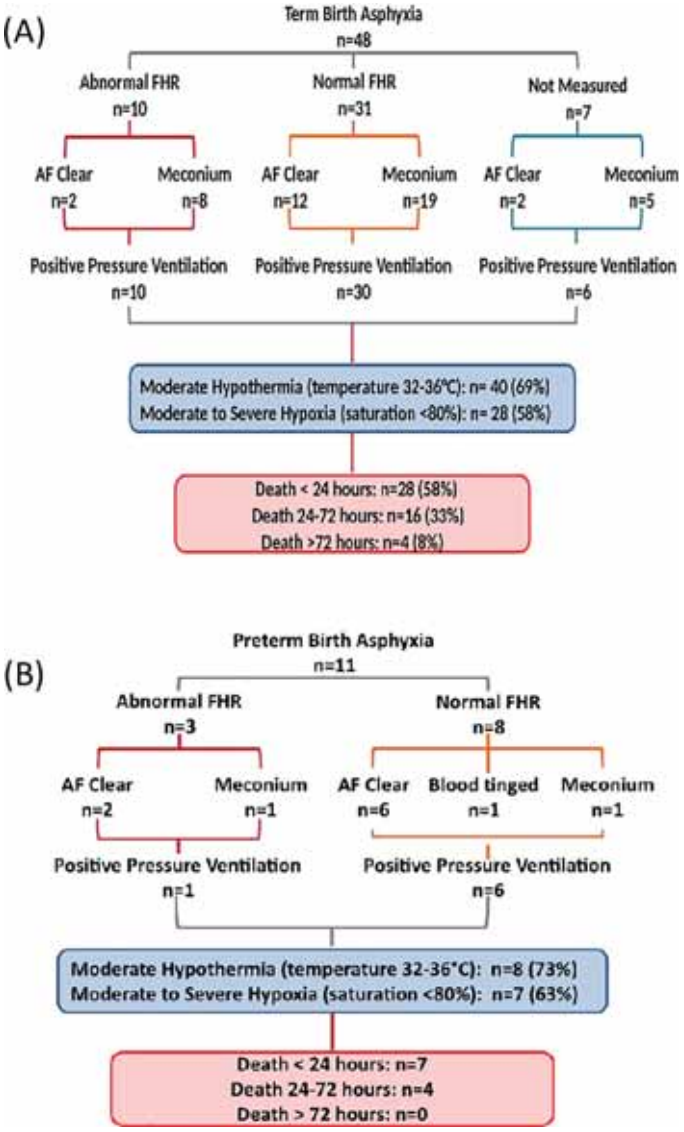

Fig 2. Perinatal characteristics, hypothermia and hypoxia and timing of death in infants with birth asphyxia. (A) Term infants. (B) Preterm infants. Abbreviations: FHR, foetal heart rate; AF, amniotic fluid.

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Characteristics of newborns who died versus survivors

Newborns who died (n = 124) compared to those who survived (n = 547), were more likely to be male (p = 0.019), have a lower 1-minute (p = 0.01) and 5-minute Apgar score <7

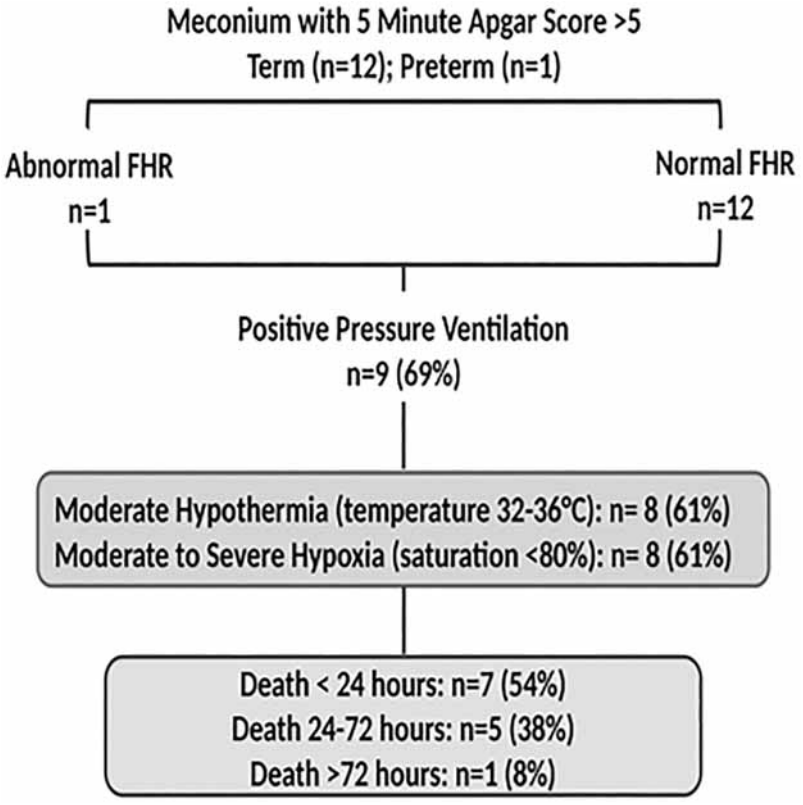

Fig 3. Perinatal characteristics, presence of hypothermia and hypoxia in infants with meconium aspiration syndrome. Abbreviations: FHR, foetal heart rate.

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($p = 0.001$), have a lower admission temperature ($p<0.001$), lower oxygen saturation ($p<0.001$), more likely to receive supplemental oxygen administration ($p<0.001$), and higher random blood glucose levels ($p = 0.04$) (Table 2). Mode of delivery and indication for caesarean section were the same between those who died and survivors.

Additional analysis of term newborns only (excluding congenital malformations) was performed. Term newborns who died ($n = 63$) compared to those who survived (n = 353), were more likely to have thick meconium (p<0.001), have a 5 minute Apgar score <7 ($p<0.001$), have received positive pressure ventilation in the delivery room ($p<0.001$) and have severe hypoxia during admission ($p<0.001$) (Table 3).

Logistic regression model of independent predictors of death for all admitted newborns and a subgroup of term newborns (excluding newborns with congenital malformations) is shown in Tables 4 and 5.

An Apgar score <7 at 5 minutes ($p = 0.005$), oxygen saturation on admission ($p = 0.001$) and birth weight ($p = 0.036$) were associated with increased odds of death in the final model

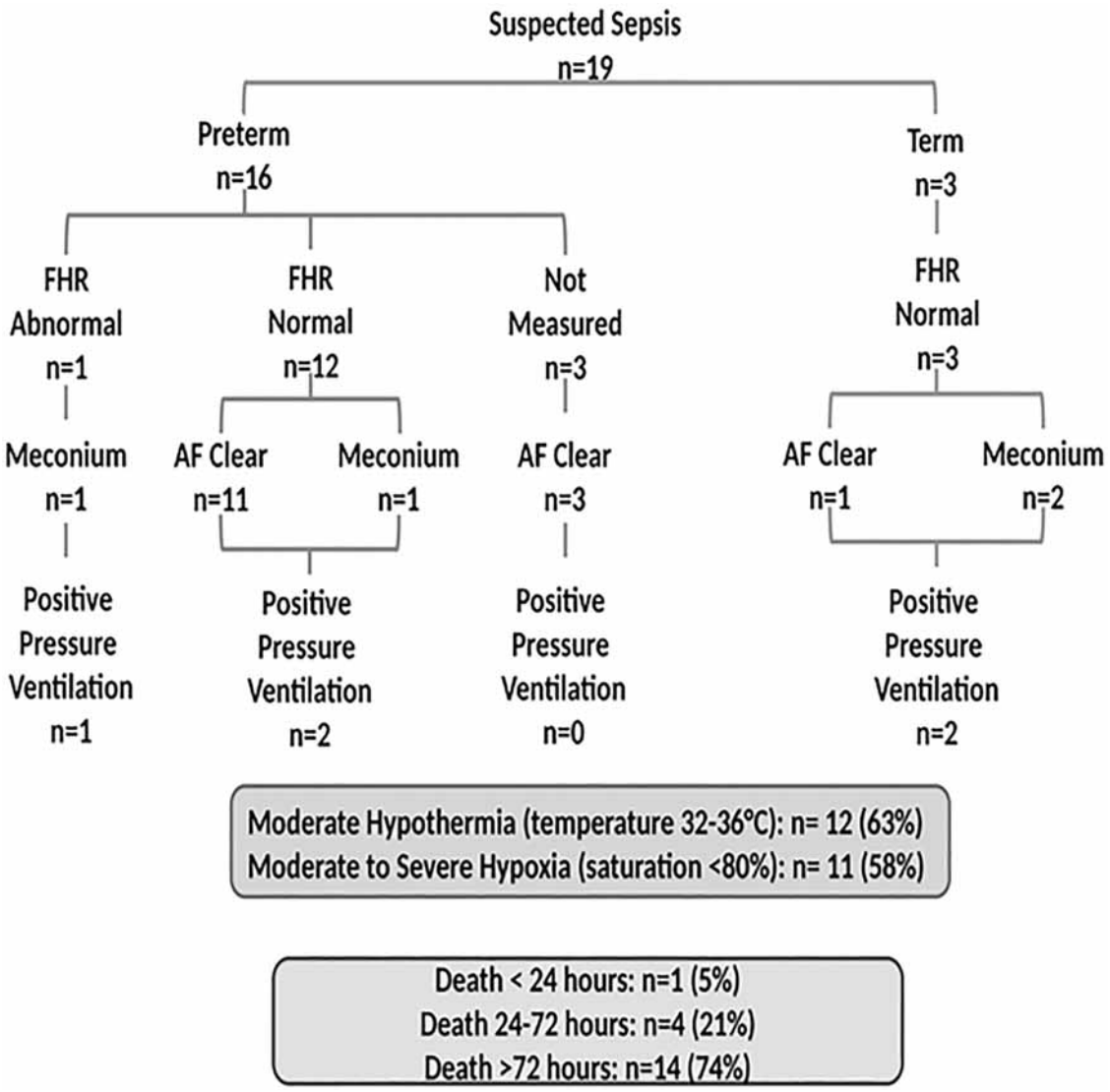

Fig 4. Perinatal characteristics, presence of hypothermia and hypoxia and timing of death in preterm infants. Abbreviations: FHR, foetal heart rate; AF, amniotic fluid.

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for all admitted neonates. Temperature was not included in the model because of missing data points (Table 4). The odds of dying versus survival increased 4.5 fold ($p = 0.010$) with positive pressure ventilation, 3.6 fold ($p = 0.006$) with a 5 minute Apgar Score <7, and 4.6 fold ($p = 0.001$) with an admitted saturation <60% among term newborns (Table 5).

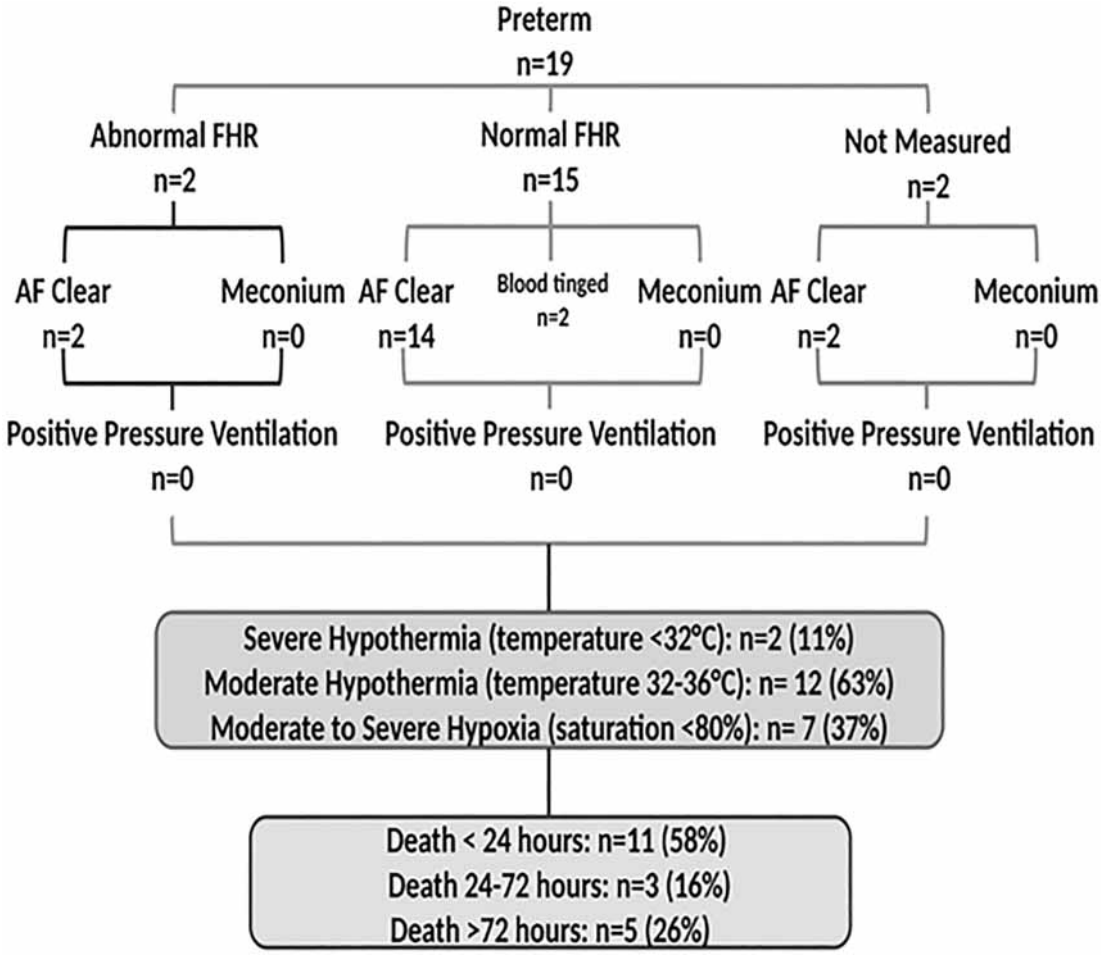

Fig 5. Perinatal characteristics, hypothermia and hypoxia and timing of death in infants with presumed/suspect sepsis. Abbreviations: FHR, foetal heart rate; AF, amniotic fluid.

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Discussion

This report highlights the major contributors of neonatal mortality in a low resource rural setting in Northern Tanzania. The findings are consistent with prior reports indicating that BA is the commonest cause of death, with prematurity and its attendant complications, presumed/suspect sepsis, MAS and congenital abnormalities as other important contributing factors. In addition, term newborns who died were 3.7 old more likely to have received positive pressure ventilation in the delivery room, 3.6 fold more likely to have an initial saturation <60% and more likely to present with moderate hypothermia upon admission to the neonatal unit compared to term survivors.

Table 2. Comparison of perinatal characteristics among newborns who died versus survivors within first 7 days.

	Dead *n* = 124	Survived *n* = 547	*P*-value
Birth weight (grams) (IQR)	2522 (1740–3010)	2640 (1930–3200)	0.07[a]
Gestational age (weeks) (IQR)	37 (32–40)	37 (34–40)	0.55 [a]
Antenatal care attendance			
Yes	122 (98)	539 (99)	
No	2 (2)	7 (1)	0.77[c]
Antenatal complications			
Yes	6 (5)	30 (5)	
No	118 (95)	516 (95)	0.67[b]
FHR during labour			
Normal	92 (75)	424 (78)	
Abnormal/not detected	16 (13)	60 (11)	
Not measured	15 (12)	62 (11)	0.76[b]
Amniotic fluid colour			
Normal	69 (56)	333 (61)	
Meconium stained	52 (42)	202 (37)	
Blood stained	3 (2)	12 (2)	0.56[b]
Obstetric complication			
Yes	16 (13)	81 (15)	
No	108 (87)	465 (85)	0.58[b]
Mode of delivery			
Vaginal	71 (58)	335 (61)	
Caesarean section	52 (42)	211 (39)	0.10[b]
Gender			
Male	76 (61)	286 (52)	
Female	47 (39)	260 (48)	0.019[b]
PPV attempted			
Yes	73 (59)	241 (44)	
No	51 (41)	306 (67)	0.003[b]
Apgar score at 1 minute			
<7	69 (56)	178 (33)	
≥7	55 (44)	369 (67)	0.001[b]
Apgar score at 5 minute			
<7	39 (32)	48 (9)	
≥7	85 (68)	499 (91)	<0.001[b]
Oxygen saturation on admission			
<60%	37 (33)	32 (12)	
60–89%	52 (46)	94 (36)	
≥90%	24 (21)	132 (51)	<0.001
Initial assessment on admission			
Temperature (C)	35.1 (34.6–36.0)	35.5 (35.0–36.0)	<0.001[a]
Heart rate (beats/minute)	143 (130–158)	140 (130–154)	0.48[a]
Need for oxygen therapy (n)	93 (92)	132 (46)	<0.001[b]

(*Continued*)

Table 2. (Continued)

	Dead *n* = 124	Survived *n* = 547	*P*-value
Random blood glucose (mmol/l)	4.2 (2.4–5.5)	3.5 (2.3–4.6)	0.04[a]

Data are presented as *n* (%) unless otherwise stated

FHR, fetal heart rate; C, Celsius; PPV, positive pressure ventilation

[a] Mann-Whitney

[b] Chi-square

[c]Fisher-exact test

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BA and MAS, which were associated with 58% of all deaths, represent intrapartum related complications, likely resulting from interruption of placental blood flow. This number is underrepresented in the present study, due to exclusion of newborns who died in the delivery room within 30 minutes of birth, presumed to be associated with BA [12]. Potential pathways contributing to death in this group included severe hypoxia and moderate to severe hypothermia noted upon admission to the neonatal ward. The severe hypoxia may reflect poor respiratory effort secondary to evolving brain injury (approximately 50% presented with moderate to severe encephalopathy), ventilation/perfusion mismatch (possibly related to MAS or moderate hypothermia) or myocardial dysfunction (possibly related to hypoxia ischemia or moderate hypothermia) [18,19,20]. These newborns were much more likely to evolve to moderate to severe encephalopathy with seizures noted in 30% of cases. The constellation of these clinical

Table 3. Comparison of perinatal characteristics among term newborns who died versus survivors within first 7 days.

	Dead	Survived	*P*-value[a]
	n = 63	n = 353	
FHR during labour (n = 382)			
Normal	45 (80)	285 (87)	
Abnormal/not detected	11 (20)	41 (13)	0.115
Amniotic fluid colour (n = 306)			
Normal	17 (38)	173 (66)	
Thick meconium stained	28 (62)	88 (34)	<0.001
Apgar score at 5 minute (n = 416)			
<7	33 (52)	38 (11)	
≥7	30 (48)	315 (89)	<0.001
PPV (n = 227)			
<60%	22 (39)	21 (12)	
60–89%	19 (34)	66 (39)	
>90%	15 (27)	84 (49)	<0.001
HIE score			
Mild	11 (30)	102 (94)	
Moderate	9 (24)	7 (6)	
Severe HIE	17 (46)	0 (0)	<0.001[b]

Data is presented as *n* (%) unless otherwise stated

FHR, fetal heart rate; PPV, positive pressure ventilation; HIE, hypoxic ischemic encephalopathy

[a]Chi-square test unless stated otherwise

[b]Fisher-exact test

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Table 4. Logistic regression model of independent predictors of death among all admitted newborns.

Variables	Bivariate analysis	*P-value*	Multivariable analysis with all variables into the model	*P-value*	Multivariable analysis after backward LR elimiation	*P-value*
	OR (95%CI)		AOR (95%CI)		AOR (95%CI)	
Gestational age (weeks)	97 (0.92–1.03)	0.34	0.99 (0.87–1.13)	0.91		
Birth weight (kg)	0.79 (0.62–1.02)	0.05	0.58 (0.31–1.08)	0.08	0.64 (0.48–0.84)	0.036
Gender						
Female	1					
Male	1.47 (0.98–2.19)	0.06	1.50 (0.96–2.37)	0.07		
Foetal heart rate						
Normal	1					
Abnormal	1.30 (0.73–2.34)	0.36	1.20 (0.63–2.36)	0.55		
Amniotic fluid colour						
Normal	1		1			
Thick meconium	1.43 (0.87–2.36)	0.15	1.48 (0.67–3.26)	0.33		
PPV attempted						
No	1		1			
Yes	1.81 (1.22–2.69)	0.003	1.49 (0.68–3.24)	0.31		
Apgar score 5 minute						
≥7	1		1		1	
<7	4.76 (2.94–7.70)	<0.001	2.81 (1.17–6.70)	0.020	3.20 (1.42–7.22)	0.005
Oxygen saturation on admission						
≥90%						
60–89%	3.04 (1.75–5.28)		3.06 (1.47–6.41)	0.003	3.10 (1.50–6.43)	0.002
<60%	6.36 (3.34–12.10)		4.53 (1.92–10.71)	0.001	4.73 (2.02–11.13)	0.001

PPV, positive pressure ventilation; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; LR, logistic regression. Temperature not included in the model because of missing data

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findings in the newborns with BA likely contributed to their early death within the first 24 hours, in most infants.

MAS contributed to 10% of all presumed causes of death, which is also higher when compared to the 1.5 to 5% from previous reports [6, 21]. This may represent an over diagnosis due to the inability to obtain chest radiographs, and/or to definitely exclude other pulmonary complications such as pneumothorax, congenital pneumonia and/or concurrent infection. This high mortality rate may reflect the absence of continuous end positive pressure (CPAP) and/or mechanical ventilation, as well as an inability to intubate and potentially administer surfactant, interventions which are regarded as standard of care in developed countries [22].

The above findings offer potential opportunities for reducing mortality related to BA and/or MAS. More than half of newborns who died of BA and MAS had a normal foetal heart rate during labour determined intermittently using a fetoscope in most cases. This raises an important question whether these fetuses could have been identified with continuous foetal heart rate monitoring. The more recent availability of a continuous foetal heart rate monitor termed Moyo, may more readily identify high risk fetuses during labor [23,24]. However our group has recently shown while continuous as opposed to intermittent foetal heart rate monitoring results in the detection of more foetal heart rate abnormalities, it does not reduce the time from detection to delivery, suggesting bottlenecks in the system (i.e. lack of operating rooms and/or skilled clinical providers) [23,24]. Post-delivery, more effective resuscitation including

Table 5. Logistic regression model of independent predictors of death among term admitted newborns (excluding congenital malformations).

Variables	Bivariate analysis OR (95%CI)	*P-value*	Multivariable analysis with all variables into the model	*P-value*	Multivariable analysis after backward LR elimination	*P-value*
			AOR (95%CI)		AOR (95%CI)	
Foetal heart rate						
Normal	1		1			
Abnormal	1.69 (0.81–3.54)	0.15	1.12 (0.35–3.53)	0.84		
Amniotic fluid colour						
Normal	1		1			
Thick meconium	3.24 (1.68–6.23)	<0.001	2.36 (0.95–5.86)	0.063		
Apgar score 5 minute						
≥7	1		1			
<7	9.11 (5.01–16.58)	<0.001	3.74 (1.44–9.68)	0.006	3.61 (1.67–7.81)	0.001
PPV						
No	1		1		1	
Yes	7.35 (3.09–17.49)	<0.001	4.58(1.23–17.06)	0.023	4.00 (1.40–11.44)	0.010
Oxygen saturation						
<60%	5.8 (2.61–13.21)	<0.001	3.7 (1.24–11.10)	0.019	4.60 (1.82–11.65)	0.001

PPV, positive pressure ventilation; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; LR, likelihood ratio.

https://doi.org/10.1371/journal.pone.0222935.t005

the provision of CPAP and/or endotracheal intubation as indicated above, minimizing hypoxia and maintaining temperature in the normal range are basic first step strategies to potentially reduce early mortality [25, 26]. While both the diagnosis of BA i.e. WHO criteria of a 5-minute Apgar <7 in a non-breathing baby, and that of MAS were made clinically, without evidence of severe fetal acidemia (umbilical cord arterial pH <7.00), multiple organ failure [18,27] or radiological confirmation with MAS, we consider the constellation of clinical findings and potential basic interventions as described above, specific enough to have broad generalizability in potentially reducing early mortality.

Globally, preterm births accounts for 25% of all newborn deaths [6]. In this report, prematurity as the primary diagnosis contributed to 15% of neonatal deaths which is lower than prior Tanzanian and global studies [2, 5, 6]. Preterm newborns who died in this study did not have evidence of intrapartum related complications and their delivery room transitional phase was uneventful. However, more than half of the deaths occurred within the first 24 hours. This is most likely attributed to early respiratory distress due to surfactant deficiency, no CPAP, absence of surfactant replacement therapy and further exacerbated by moderate to severe hypothermia noted upon admission to the neonatal unit [28]. Preterm newborns are highly susceptible to infections and the majority of newborns who died of presumed/suspected sepsis were premature; these infants also had an uneventful delivery room transition. Thus, overall when all diagnoses are combined, prematurity contributed to nearly 30% of deaths in this cohort. Adopting WHO recommended interventions such as administration of antenatal corticosteroids to women who are at imminent risk of preterm labour, antibiotic administration to women with preterm premature rupture of membranes, and initiation of CPAP for newborns with RDS, could improve premature mortality in this setting [9]. In a recent publication from Tanzania, Massawe et al. reported a reduction in mortality in premature newborns of gestational age 28 to 34 6/7 weeks, after administration of antenatal corticosteroids and antibiotics, to both the mother and her newborn [29].

The rate of congenital malformation in this report of 11% is in line with WHO worldwide estimates, as well as the estimates in Tanzania of 14% [5, 6]. The contribution of congenital abnormalities to specific causes of death is probably significantly underestimated in this setting, because of the limited resources to screen with chromosomal analysis or more recent techniques such as microarray and to perform an autopsy after death.

Moderate hypothermia has been linked to an increased risk of death in a dose dependent manner [30]. In this cohort, most admitted newborns with measured temperatures were moderately hypothermic, noted in approximately two thirds of those who died. A recent study from Brazil showed that admission hypothermia was significantly associated with early neonatal deaths even in a presence of good quality newborn care [31]. Continuous improvement of thermal care immediately after birth is critically needed. Potential strategies include early skin to skin care immediately after birth [32], the introduction of overhead heaters or plastic wraps in the delivery room [33] and during transfer of newborns.

From the above it should be apparent that strategies to reduce neonatal mortality in the low-resource setting are complex, influenced by many factors. Reducing mortality due to intrapartum complications will require a multiple prong approach, targeting interventions such as enhanced foetal heart rate monitoring coupled with expedited delivery where indicated, as well as optimizing delivery room resuscitation and in particular, focusing on efforts to maintain the warmth of the newly born. The perinatal management of newborns who are born through thick MSAF requires further study in low-resource countries, with efforts directed towards enhancing respiratory support i.e. CPAP.

The findings of this study should be interpreted cautiously. First, this was a single center study with many resource limitations. Second, this study only included inborn neonates in an area where admitted outborn births are primarily premature neonates, who contribute considerably to mortality in this setting. Third, the challenges of accurate diagnosis without laboratory or radiological studies were substantial, and diagnosis relied mostly on the clinical acumen of the practitioner. Furthermore, postmortem examination to confirm causes of deaths is rare in this setting.

Conclusion

Intrapartum related complications such as BA and MAS contributed to almost two thirds of the deaths, with prematurity and presumed/suspect sepsis additional important causes. Intrapartum complications and prematurity are the main pathways leading to death in this rural setting. Hypothermia likely played a significant role in increasing mortality in this setting. Strategies to identify fetuses at high risk of intrapartum hypoxia/ischemia, coupled with timely interventions should be a priority in this setting. Implementation of WHO recommended interventions for improving preterm outcome, including improving thermal control and enhancing basic diagnostics such as completed blood count, C-reactive protein and imaging studies is critical to facilitate targeted interventions.

Supporting information

S1 Dataset. Data file.
(SAV)

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References

1. Tanzania Demographic Health Survery and Malaria Indicator. 2015.
2. Afnan-Holmes H, Magoma M, John T, Levira F, Msemo G, Armstrong CE, et al. Tanzania's Countdown to 2015: An analysis of two decades of progress and gaps for reproductive, maternal, newborn, and child health, to inform priorities for post-2015. Lancet Glob Heal. 2015; 3: e396–409
3. Lawn JE, Cousens S, Zupan J. 4 Million neonatal deaths: When? Where? Why? Lancet. 2005; 365:891–900. https://doi.org/10.1016/S0140-6736(05)71048-5 PMID: 15752534
4. Lawn JE, Blencowe H, Oza S, You D, Lee ACC, Waiswa P, et al. Every newborn: Progress, priorities, and potential beyond survival. Lancet. 2014; 384:189–205. https://doi.org/10.1016/S0140-6736(14)60496-7 PMID: 24853593
5. World Health Organization. Global Health Observatory (GHO): Data Repository. GHO. 2018. Available from: http://apps.who.int/gho/data/node.home
6. Mmbaga BT, Lie RT, Olomi R, Mahande MJ, Kvåle G, Daltveit AK. Cause-specific neonatal mortality in a neonatal care unit in Northern Tanzania: a registry based cohort study. BMC Pediatr. 2012; 12:116. https://doi.org/10.1186/1471-2431-12-116 PMID: 22871208
7. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. Intensive care for extreme prematurity-moving beyond gestational age. N Engl J Med. 2008; 358:1672–81. https://doi.org/10.1056/NEJMoa073059 PMID: 18420500
8. Straughn HK, Goldenberg RL, Tolosa JE, Daly S, Codes J De, Festin MR. Birthweight-specific neonatal mortality in developing countries and obstetric practices. Int J Gynaecol Obstet. 2003; 80:71–8. https://doi.org/10.1016/s0020-7292(02)00309-0 PMID: 12527467
9. World Health Organization. WHO Recommendations on Interventions to Improve Preterm Birth Outcomes. 2015. Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/preterm-birth-guideline/en/%5Cn
10. Mdoe PF, Ersdal HL, Mduma E, Perlman JM, Moshiro R, Wangwe PT, et al. Intermittent fetal heart rate monitoring using a fetoscope or hand held Doppler in a rural Tanzania: a randomized controlled trial. BMC Pregnancy Childbirth. 2018; 18:134. https://doi.org/10.1186/s12884-018-1746-9 PMID: 29728142
11. The American Academy of of Pediatrics. Helping Babies Breathe. 2009. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/Helping-Babies-Breathe.aspx
12. Ersdal HL, Eilevstjønn J, Linde JE, Yeconia A, Mduma ER, Kidanto H, et al. Fresh stillborn and severely asphyxiated neonates share a common hypoxic-ischemic pathway. Int J Gynecol Obstet. 2018; 141:171–180.
13. World Health Organization. Maternal, Newborn, Child and Adolescent Health. Essential newborn care. World Health Organization. 2010. http://www.who.int/maternal_child_adolescent/documents/newborncare_course/en/
14. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, et al. Controversies Regarding Definition of Neonatal Hypoglycemia: Suggested Operational Thresholds. Pediatrics. 2000; 105:1141–5. https://doi.org/10.1542/peds.105.5.1141 PMID: 10790476
15. Thompson CM, Puterman AS, Linley LL, Hann M, van der Elst CW, Molteno CD, et al., The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr, 1997. 86(7): p. 757–61. https://doi.org/10.1111/j.1651-2227.1997.tb08581.x PMID: 9240886
16. Ohlin A, Björkqvist M, Montgomery SM, Schollin J. Clinical signs and CRP values associated with blood culture results in neonates evaluated for suspected sepsis. Acta Paediatr. 2010; 99:1635–40. https://doi.org/10.1111/j.1651-2227.2010.01913.x PMID: 20560896

17. Griffin MP, Lake DE, O'Shea TM, Moorman JR. Heart rate characteristics and clinical signs in neonatal sepsis. Pediatr Res. 2007; 61:222–7. https://doi.org/10.1203/01.pdr.0000252438.65759.af PMID: 17237726

18. Perlman JM, Tack ED, Martin T, Shackelford G, Amon E. Acute Systemic Organ Injury in Term Infants After Asphyxia. Am J Dis Child.1989; 143:617–20 https://doi.org/10.1001/archpedi.1989.02150170119037 PMID: 2718998

19. Kiley JP, Eldridge FL, Millhorn DE. The effect of hypothermia on central neural control of respiration. Respir Physiol 1984; 58:295–312 https://doi.org/10.1016/0034-5687(84)90006-9 PMID: 6441983

20. Askin D. Newborn adaptation to extrauterine life. In: Simpson K. R. & Creehan P. A.. AWHONN's Perinatal Nursing. (3rd ed.). Philadelphia: Lippincott Williams & Wilkins.

21. Vain NE, Szyld EG, Prudent LM, Wiswell TE, Aguilar AM, Vivas NI. Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: Multicentre, randomised controlled trial. Lancet. 2004; 364:597–602 https://doi.org/10.1016/S0140-6736(04)16852-9 PMID: 15313360

22. Wiswell TE, Henley MA. Intratracheal suctioning, systemic infection, and the meconium aspiration syndrome. Pediatrics. 1992; 89:203 PMID: 1734384

23. Mdoe PF, Ersdal HL, Mduma E, Moshiro R, Dalen I, et al. Randomized controlled trial of continuous Doppler versus intermittent fetoscope fetal heart rate monitoring in a low-resource setting. Int J Gynaecol Obstet. 2018; 143:344–350. https://doi.org/10.1002/ijgo.12648 PMID: 30120775

24. Kamala BA, Ersdal HL, Dalen I, Abeid MS, Ngarina MM, et al. Implementation of a novel continuous fetal Doppler (Moyo) improves quality of intrapartum fetal heart rate monitoring in a resource-limited tertiary hospital in Tanzania: An observational study. PLoS One. 2018; 13:e0205698 https://doi.org/10.1371/journal.pone.0205698 PMID: 30308040

25. Ersdal HL, Mduma E, Svensen E, Perlman JM. Early initiation of basic resuscitation interventions including face mask ventilation may reduce birth asphyxia related mortality in low-income countries. A prospective descriptive observational study. Resuscitation. 2012; 83:869–73. https://doi.org/10.1016/j.resuscitation.2011.12.011 PMID: 22198423

26. Moshiro R, Ersdal HL, Mdoe P, Kidanto HL, Mbekenga C. Factors affecting effective ventilation during newborn resuscitation: a qualitative study among midwives in rural Tanzania. Glob Health Action. 2018; 11:1423862. https://doi.org/10.1080/16549716.2018.1423862 PMID: 29343190

27. Perlman JM, Risser R. Severe fetal acidemia: Neonatal neurologic features and short-term outcome. Pediatr Neurol.1993; 9:277–82 https://doi.org/10.1016/0887-8994(93)90063-i PMID: 8216539

28. Patel Ravi M, Sarah Kandefer, Walsh Michele C., Bell Edward F., Carlo Waldemar A., et al. Causes and Timing of Death in Extremely Premature Infants from 2000 through 2011N Engl J Med 2015; 372:331–340

29. Massawe A, Kidanto HL, Moshiro R, Majaliwa E, Chacha F, Shayo A, et al. A care bundle including antenatal corticosteroids reduces preterm infant mortality in Tanzania a low resource country. PLoS One. 2018; 13:e0193146 https://doi.org/10.1371/journal.pone.0193146 PMID: 29513706

30. Laptook AR, Salhab W, Bhaskar B. Admission Temperature of Low Birth Weight Infants: Predictors and Associated Morbidities. Pediatrics. 2007; 119:e643–9. https://doi.org/10.1542/peds.2006-0943 PMID: 17296783

31. de Siqueira Caldas JP, Ferri WAG, Marba STM, Aragon DC, Guinsburg R, et al. Eur J Pediatr (2019). https://doi.org/10.1007/s00431-019-03386-9

32. Mccall EM, Alderdice F, Halliday HL, Vohra S, Johnston L. Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews. 2018. Issue 2. Art. No.: CD004210. DOI:

33. Leadford AE, Warren JB, Manasyan A, Chomba E, Salas AA, Schelonka R, et al. Plastic Bags for Prevention of Hypothermia in Preterm and Low Birth Weight Infants. Pediatrics. 2013; 132:e128–34 https://doi.org/10.1542/peds.2012-2030 PMID: 23733796

Paper II

PLOS ONE

RESEARCH ARTICLE

Predictors of death including quality of positive pressure ventilation during newborn resuscitation and the relationship to outcome at seven days in a rural Tanzanian hospital

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Abstract

Background

Effective positive pressure ventilation (PPV) of non-breathing newborns is crucial in facilitating cardio-respiratory adaptation at birth. Identifying predictors of death in newborns receiving PPV is important in order to facilitate preventative strategies.

Objective

The objective of this study was to determine the perinatal predictors of death including the quality of PPV administered among admitted newborns.

Methods

An observational study of admitted newborns who received PPV after birth was conducted. Research assistants observed all deliveries and recorded perinatal events on data collection forms. Measured heart rate (HR) and ventilation parameters were then compared between newborns who died and survivors.

Results

Newborns ($n = 232$) were studied between October 2014 and November 2016. Newborns who died ($n = 53$) compared to survivors ($n = 179$) had more fetal heart rate (FHRT) abnormalities (12/53 vs 19/179; $p = 0.03$); lower initial HR (<100 beats/minute) at start of PPV (44/48 vs 77/139; $p<0.001$); and a longer time for HR to increase >100 beats/minute from birth (180 vs 149 seconds; $p = 0.07$). Newborns who died compared to survivors took longer time (14 vs 4 seconds; $p = 0.008$) and more inflations (7 vs 3; $p = 0.006$) to achieve an expired

of the report, or in the decision to submit the paper for publication.

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volume (V_t) of 6 ml/kg, respectively. Median delivered V_t during the first 60 seconds of PPV was less in newborns who died compared to survivors (5 vs 6 ml/kg; $p = 0.12$). Newborns who died proceeded to severe encephalopathy (15/31 vs 1/59; $p<0.001$) compared to survivors.

Conclusion

Depressed newborns who proceeded to death compared to survivors, exhibited delayed HR response to PPV which may partly reflect FHRT abnormalities related to interruption of placental blood flow, and/or a timely delay in establishing adequate V_t. Depressed newborns progressed to moderate/severe encephalopathy. Improving FHRT monitoring to identify fetuses at risk for expedited delivery, coupled with optimizing delivery room PPV might decrease mortality in this setting.

Introduction

Approximately 23% of newborn deaths in Sub-Saharan Africa are related to intrapartum hypoxia/ischemia [1]. Transition from intra-uterine to extra-uterine life is a crucial phase for newborns. In Tanzania, approximately 15 percent of newborns will need some assistance to make this transition at birth; six percent require positive pressure ventilation (PPV) [2]. Therefore, provision of effective PPV is important to improve outcomes for those who fail to initiate spontaneous breathing at birth.

The aim of initial PPV is to establish functional residual capacity (FRC) [3]. The establishment of FRC is accompanied by an increase in pulmonary blood flow and an increase in heart rate (HR), indicating successful gaseous exchange [4]. Thus, an increase in HR is considered to be the most important clinical indicator of effective PPV, during newborn resuscitation [5,6]. The optimal volume during ventilation is unknown, however, an expired tidal volume (V_t) between 3.3 and 10.5ml/kg is normally generated during spontaneous breathing at birth [7–9] and during face mask ventilation after birth [10,11]. We recently showed that a minimum V_t of 6 ml/kg is required to produce an increase in HR during PPV [12].

The commonest reason for a HR <100 beats/minute (BPM) upon delivery is secondary to an interruption of placental blood flow, often loosely termed "birth asphyxia". If the interruption of blood flow is brief, most neonates are presumed to be in primary apnoea and will invariably respond to stimulation/suction with an increase in HR [12]. If the interruption in blood flow is more prolonged, the neonate is likely to be in secondary apnoea and will be less likely to respond to stimulation alone, invariably requiring PPV to correct the bradycardia. The International Liaison Committee of Resuscitation (ILCOR) recommends that PPV should be initiated on a newborn with a HR <100 BPM [6]. Few studies have documented changes in HR during PPV in relation to outcome as a measure of efficacy of ventilation. Most of the studies were performed in premature newborns and in the developed world [13,14].

When interruption of placental blood flow is prolonged or severe, the risk for hypo-perfusion to the brain is substantial. Such neonates will present with apnoea, and prolonged bradycardia, even with effective PPV [15]. The risk for subsequent hypoxic ischaemic encephalopathy (HIE) is markedly increased. Several postnatal factors are known to exacerbate ongoing neuronal injury caused by birth asphyxia, including hypothermia/hyperthermia, seizures and hypoglycaemia [16,17]. Monitoring and targeted management strategies during the first hours after birth, is crucial for enhancing outcome of asphyxiated babies.

Investigating factors affecting outcome of newborns receiving PPV could provide important insight with regards to future resuscitation training, particularly as it relates to labour monitoring and assessment as well as the post-delivery care of newborns in low-resource settings. The objective of this study was to determine the perinatal predictors of death including the quality of PPV administered in the delivery room to newborns following admission to a newborn area.

Methods

This was an observational study on newborn resuscitation at Haydom hospital, a rural hospital with an estimated 4500 deliveries annually, providing comprehensive emergency obstetric care services 24 hours a day. Midwives conducted all deliveries including labour monitoring using the partograph as the assessment tool. Intermittent FHRT monitoring was performed using either a Pinard stethoscope or Doppler depending on the preference of the midwife. Normal FHRT was defined as between 120–160 BPM and FHRT persistently outside this normal range was considered abnormal. Newborn resuscitation was also conducted by midwives trained in Helping Babies Breathe, a resuscitation program tailored for the low resource setting [18]. Research assistants ($n = 14$) were trained to observe and document every delivery in the labour ward and theatre. All resuscitations were performed using Newborn Resuscitation Monitors (NRM, Laerdal Global Health, Stavanger, Norway; Fig 1), a research tool developed for the purpose of recording resuscitations.

The hospital's newborn area accommodates 10–15 patients. Admission criteria include prematurity (gestational age <34 weeks), five-minute Apgar score <7, fever (>38˚C) and signs of respiratory compromise, i.e., intercostal, subcostal retractions, or grunting. The newborn area offers antibiotics, oxygen therapy, phototherapy, and intravenous fluids. No mechanical ventilation or continuous positive airway pressure is available. From October 2014 to November 2016, admitted newborns who received PPV in the delivery room were consecutively enrolled, and followed-up until discharge or death within the first seven days. Information about admitted newborns in the newborn area was captured using a data collection form. Ventilated newborns who died in the delivery room were excluded from this study because they have been reported elsewhere [15].

HR and expired tidal volume (V_t) measurements

HR measurements were recorded and displayed on the screen in front of the providers by NRMs installed in all delivery rooms and the operating theatre. The monitor comprised a self-inflating bag without positive end expiratory pressure (PEEP), and an electrocardiogram (ECG) dry-electrode-based HR sensor [19]. The application of the ECG based sensor takes approximately 3 seconds to complete, and a HR is detected within approximately 5 seconds [19]. All newborn resuscitators were fitted with ventilation sensors between the bag and the mask, measuring flow, pressure and CO_2. The flow sensors, using hot-wire anemometer technology, measured flow during expiration, and volume was calculated by flow signal integration. Mask leakage was calculated by the difference between inspiratory and expiratory volume. Time in seconds for HR to reach 100 BPM and V_t, was downloaded from the NRM and extracted using Q-CPR Review 3.1.2.2 (Laerdal Medical, Stavanger, Norway). An episode of PPV was defined as time from the start of PPV to the end of PPV. Resuming PPV after a pause of >5 seconds was considered to be the start of a new ventilation sequence (Fig 1). Ventilation fraction was defined as time spent during actual ventilation, and ventilation frequency was defined as inflations per minute. We considered V_t of 6 ml/kg as the minimum volume required to increase HR during PPV [12]. We therefore defined quality of ventilation as a V_t of

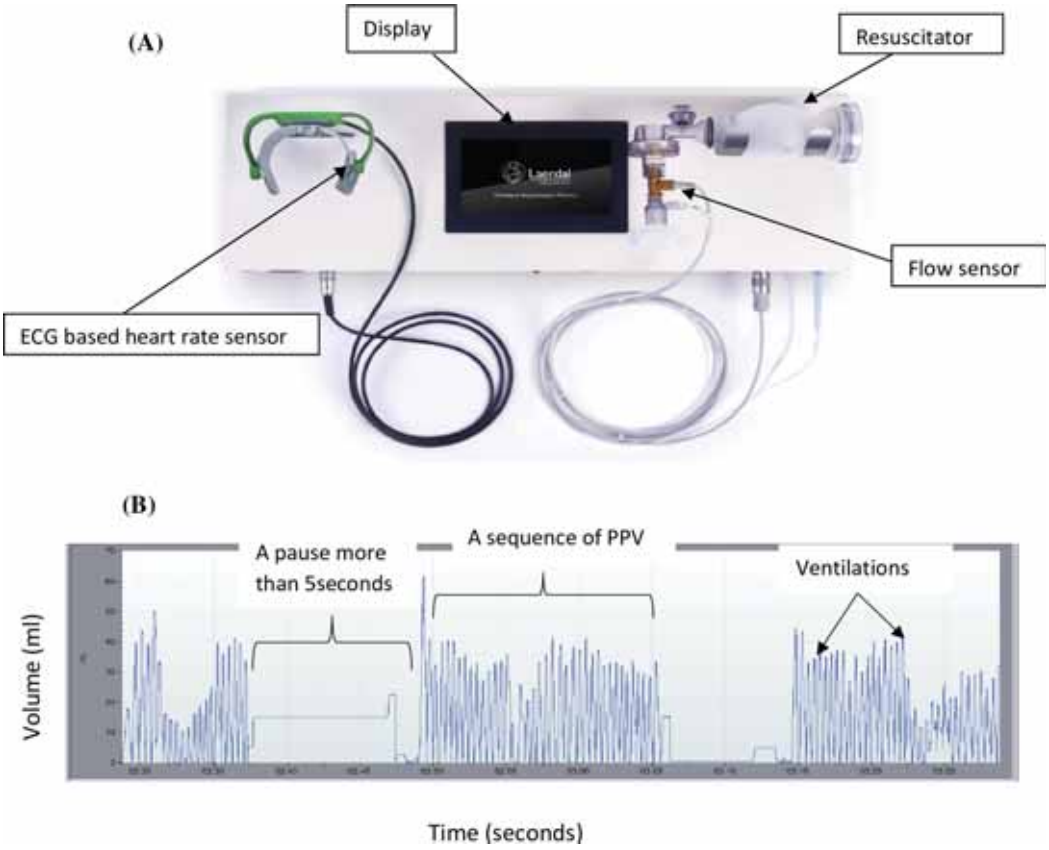

Fig 1. Newborn Resuscitation Monitor with a dry-electrode heart rate sensor, a resuscitator and signal output. (A) Monitor with ECG-based heart rate sensor and a resuscitator with flow sensor. (B) Volume signal curve extracted from the monitor.

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6 ml/kg together with a rapid increase in HR above 100 BPM within 15 to 30 seconds after commencing PPV [4].

Initial assessment during admission

Management of newborns followed the principles outlined in the WHO Essential Newborn Care guidelines [20]. Axillary temperature and blood glucose measurements were obtained using a digital thermometer and commercial glucometer, respectively, within 30 minutes of admission. Hypoglycemia, defined as blood glucose below 2.5 mmol/L [21], was treated with intravenous bolus 3 ml/kg 10% dextrose followed by feeding or maintenance with 10% dextrose. Severity of encephalopathy was classified using Thompson's Hypoxic Ischaemic Encephalopathy (HIE) score [22]. Newborns scoring 1–10 were classified as mild HIE, 11–14 as moderate HIE, and 15–22 as severe HIE. Neonatal seizures were defined as paroxysmal, repetitive movements of the hands, face, feet, eyes or mouth. Reported seizures were those noted by

the health care worker or the mother, both of whom may have not been present throughout. Seizures, if detected, were treated with intravenous Phenobarbital at a loading dose of 20 mg/kg, followed by maintenance dose of 5 mg/kg/day. Prophylactic antibiotics (ampicillin 50 mg/kg/day and gentamycin 4 mg/kg/day) were given to newborns with moderate and severely HIE for at least 48 hours because of the inability to exclude infections in this setting.

Data analysis

Categorical data were summarized as numbers and percentages, and continuous data as means and standard deviations (SD) or medians and interquartile range (IQR) as appropriate. Chi-square tests were used to test for differences in categorical variables, and Mann-Whitney *U* or *t*-tests, as appropriate, were used to test for differences in continuous variables. Multivariable logistic regression analysis was then used to model how various variables influenced the risk of death. Variables with $p < 0.20$ in the univariable analyses were included in the multivariable analysis using a stepwise backward elimination method, with the retention of predictors with $p < 0.05$. The final retained variables were then entered into the model again and results are presented as Odds Ratio (OR) with 95% confidence intervals (CIs). Variables obtained on initial assessment during admission were entered into a separate model because of missing data. Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, N.Y. USA).

Ethical clearance

This study was approved by the National Institute of Medical Research in Tanzania and the Regional Committee for Medical and Health Research Ethics, Western Norway. All mothers gave verbal informed consent after being given information about the study by the attending midwife. The midwife then signed the consent on behalf of the mother. We were allowed to obtain verbal consent because some of the women came in labour and the high illiteracy rate in this area.

Results

General characteristics

During the study period, there were 8139 deliveries of mean birth weight 3287±529 grams and gestation age 39±2 weeks. A total of 1387 (18%) newborns received stimulation and/or suctioning, and 514 (6.3%) received PPV. Of these, 232 newborns were admitted and included in the study; 53 (23%) died within seven days (Fig 2). Of those who died, 15 (28%) died within 24 hours, and 75% died within the initial 72 hours of life. Among the newborns receiving PPV, 282 were not included; 17 died in the delivery room, and 265 recovered and stayed with the mother (were not admitted). The 17 newborns who died in the delivery room had mean birth weight 2931±551 grams and gestational age 37±3 weeks. The characteristics of this cohort have been reported previously [15]. Due to equipment malfunction ($n = 15$) and missing data ($n = 21$), ventilation parameters were only available for 196 admitted newborns (four of the 36 newborns with missing data died).

Newborn characteristics and outcome of newborns who died versus survivors

Comparison of newborn characteristics between those who died and survivors through day 7 of life are shown in Table 1. Newborns who died as compared to survivors had more FHRT abnormalities during labour, 5-minute Apgar score <7 and a lower HR (<100 BPM) at the

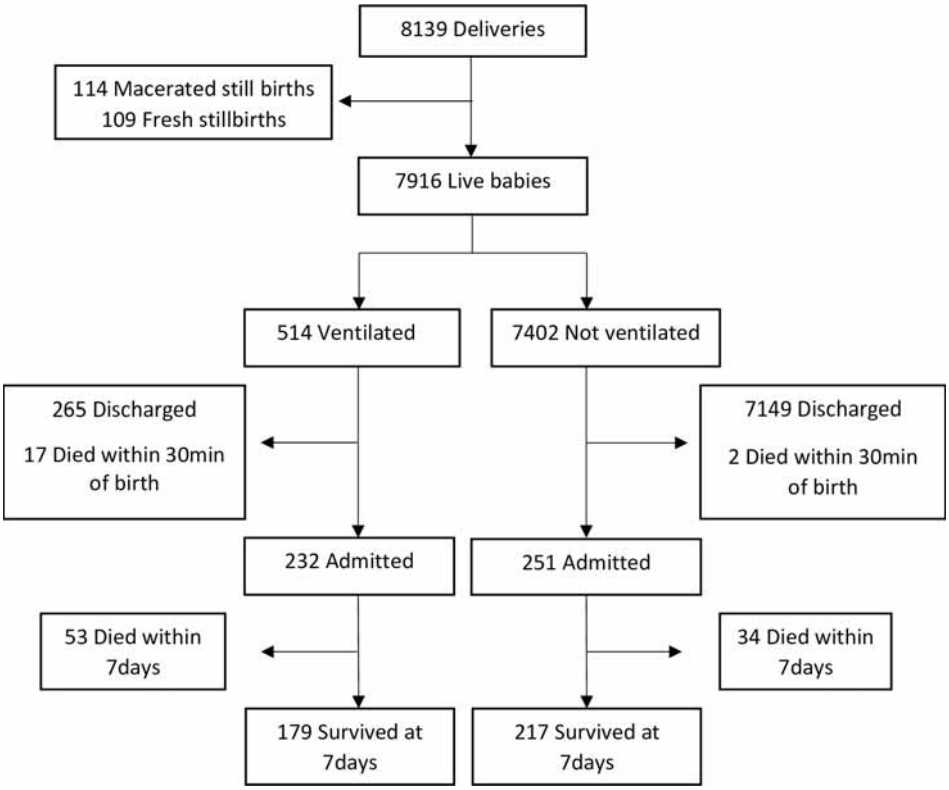

Fig 2. Flow diagram of patient recruitment.

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start of PPV. At the end of ventilation, 13/121 (11%) newborns had a HR <100 BPM, of whom 9 (70%) died. Newborns who died as compared to those who survived had significantly lower temperature, lower oxygen saturation, higher blood glucose, and progressed to severe encephalopathy (Table 1). Newborns who died were likely to have seizures, and to receive Phenobarbital and oxygen therapy. Of the newborns who died, 29/53 (55%) did so within first 24 hours of life. The most common presumptive cause of death was severe HIE. Mode of delivery ($p = 0.35$), gestational age ($p = 0.20$) and birthweight ($p = 0.29$) were comparable for both groups.

HR responses and ventilation parameters in relation to outcome

Factors related to newborn responses to PPV in relation to outcome are summarized in Table 2. Newborns who died compared to those who survived took a longer time to reach HR >100 BPM ($p = 0.007$). Newborns who died compared to those who survived received less volume (ml/kg) during the first 60 seconds of PPV, i.e., 5 versus 6 ($p = 0.13$), and more volume during the whole episode of PPV, i.e., 9 versus 7 ($p = 0.41$) (Table 2). It took a longer time to achieve a $V_t \geq 6$ ml/kg for those newborns who died compared to those who survived, i.e., a

Table 1. Comparison of newborn characteristics among babies who survived versus dead within first 7 days.

	Survived *n* = 179	Dead *n* = 53	*P*-value
	mean±SD or *n* (%)	*mean±SD* or *n* (%)	
Gestational age (weeks)	38.0±2.5	37.0±3.0	0.20[b]
Birth weight (grams)	2910±600	2811±620	0.29[b]
FHRT during labour			
Normal	148 (83)	35 (66)	0.030[a]
Abnormal/not detected	19 (11)	12 (23)	
Not measured	12 (7)	6 (11)	
Apgar score at 5th minute			
<7	34 (19)	24 (45)	<0.001[a]
≥7	145 (81)	29 (55)	
Initial HR recorded (BPM)	99 (64–148)	61 (53–80)	<0.001[c]
HR at the start of ventilation			
<100 BPM	77 (55)	44 (92)	<0.001[a]
≥100 BPM	62 (45)	4 (8)	
HR at the end of ventilation			
<100 BPM	4 (3)	9 (18)	<0.001[a]
≥100 BPM	134 (97)	39 (82)	
Initial assessment and treatment on admission			
Temperature (degree Celsius)[d]	35.2 ± 0.9	34.7 ± 1.0	0.004[b]
Oxygen saturation (%)[e]	81.0 ± 18.0	69.0 ± 22.0	0.004[b]
Oxygen supplement[f]	53 (62)	33 (92)	0.001[a]
Blood glucose (mmol/L)[g]	3.9 ± 2.1	4.6 ± 2.9	0.23[b]
HIE score on admission (*n* = 90)			
Normal	13 (22)	1 (3)	<0.001[a]
Mild	38 (64)	9 (29)	
Moderate	7 (12)	6 (19)	
Severe	1 (2)	15 (48)	
Seizures (*n* = 124)			
Yes	9 (10)	15 (40)	<0.001[a]
No	78 (90)	22 (50)	
Phenobarbital	26 (30)	20 (54)	0.012[a]

FHR, fetal heart rate; SVD, spontaneous vaginal delivery; CS, caesarean section; HR, heart rate; BPM, beats/minute.

[a]chi-square.

[b]t-test.

[c]Mann-Whitney *U* test.

[d]missing value *n* = 127.

[e]missing value; *n* = 103.

[f]missing value *n* = 109.

[g]missing value; n = 1.

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median value of 14 versus 4 seconds ($p = 0.008$), respectively. The number of ventilations to achieve a TV >6 ml/kg was greater in the infants who died compared to those who survived i.e., median of 7 vs 3 ($p = 0.006$). Newborns who died were ventilated for a much longer time compared to survivors, i.e., 402 versus 230 seconds ($p = 0.001$), respectively (Table 2). There was less mask leakage in newborns who died compared to those who survived ($p = 0.027$).

Results of the univariable and multivariable analyses are shown in Tables 3 and 4. Abnormal FHRT ($p = 0.018$), 5-minute Apgar score <7 ($p \leq 0.001$), HR at the start of PPV ($p \leq 0.001$),

Table 2. Responses of newborns to positive pressure ventilation in relation to outcome survived vs dead within first 7 days.

Variables	Survived n = 179 Median (IQR) or *n*(%)	Dead n = 53 Median IQR or *n*(%)	*P*-value
Stimulation (yes)	179 (100%)	53 (100%)	
Suction (yes)	176 (98%)	44 (83%)	0.92[b]
Time from birth to cord clamp (s)	25 (11–57)	18 (10–38)	0.19[a]
Time from birth to application of HR sensor (s)	108 (76–158)	116 (73–140)	0.52[a]
Time from birth to detection of initial HR (s)	113 (85–158)	116 (83–152)	0.92[a]
Time from birth to start PPV (s)	115 (85–17)	117 (85–147)	0.35[a]
Time from birth to HR increase >100 BPM (s)[c]	149 (105–208)	180 (119–235)	0.07[a]
V_t first 60s of PPV (ml/kg)	6 (4–12)	5 (3–10)	0.12[a]
V_t whole episode of PPV (ml/kg)	8 (5–12)	9 (5–14)	0.36[a]
Vol/min first 60s of PPV (ml/min)	896 (429–1528)	781 (375–1414)	0.14[a]
Vol/min whole episode of PPV (ml/min)	1140 (643–1876)	1389 (731–1900)	0.41[a]
Time from start PPV to V_t >6 ml/kg (s)	4 (1–18)	14 (2–31)	**0.008**[a]
Number of ventilations before >6 ml/kg	3 (1–10)	7 (2–20)	**0.006**[a]
Time used ventilating during first 60s (s)	40 (28–55)	44 (31–54)	0.57[a]
PPV frequency during first 60s (inflations/minute)	45 (37–57)	50 (40–59)	0.19[a]
PPV frequency during whole episode (inflations/minute)	44 (36–55)	52 (39–60)	0.25[a]
Mask leak during ventilation (%)	40 (26–54)	33 (21–55)	**0.027**[a]
Time of whole episode of PPV (s)	230 (104–466)	402 (203–785)	<**0.001**[a]

PPV, positive pressure ventilation; Vol/min, volume per minute; s, seconds; HR, heart rate; BPM, beats/minute; V_t, expired tidal volume; IQR, inter-quartile range.

[a]Mann-Whitney *U* tests.

[b]chi-square.

All ventilation parameters $n = 196$ except [c]median time from birth to HR to increase >100 BPM $n = 127$.

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HR at the end of PPV ($p \leq 0.001$), mask leakage ($p = 0.026$) and median time of PPV ($p \leq 0.001$), were all independently associated with increased odds of death (Table 3). When adjusted for all variables in the final model, abnormal FHRT ($p = 0.019$), HR at the end of PPV ($p = 0.002$) and median duration of PPV ($p = 0.001$) were all associated with increased odds of death. Postnatal predictors of death are summarized in Table 4. Admission temperature ($p = 0.003$), seizures ($p < 0.001$), oxygen saturation ($p = 0.003$) and moderate/severe HIE ($p < 0.001$) were independently associated with death within first seven days. When adjusted for the rest of the variables in the model, moderate/severe HIE ($p < 0.001$) was significantly associated with risk of death.

Discussion

The data in this report demonstrated that newborns who died within the first week of life as opposed to survivors exhibited more FHRT abnormalities in utero, lower initial HR as well as a lower HR following PPV, and received a longer duration of PPV. In addition, newborns who died were more likely to be depressed at birth, have a lower body temperature on admission to the neonatal area, and progress to moderate/severe encephalopathy and seizures.

Table 3. Logistic regression model for independent predictors of death within first 7 days among admitted newborns.

Variables	Univariable analysis OR (95% CI)	*P* value	Multivariable analysis with all variables into the model AOR (95% CI)	*P* value	Multivariable analysis after backward LR elimination AOR (95% CI)	*P* value
FHRT during labour						
Normal	1		1		1	
Abnormal/not detected	2.67 (1.19–6.01)	0.018	3.94 (1.25–12.40)	0.019	3.15 (1.21–8.19)	0.018
Not measured	2.11 (0.74–6.02)	0.16	1.29 (0.23–7.11)	0.77	3.09 (0.93–10.23)	0.06
Apgar score						
≥7	1		1			
<7	3.53 (1.83–6.81)	<0.001	2.19 (0.84–5.01)	0.11		
HR at start of PPV						
≥100	1		1			
<100	8.86 (3.02–25.99)	<0.001	1.85 (0.18–19.63)	0.61		
HR at end of PPV						
≥100 BPM	1		1		1	
<100 BPM	7.54 (2.20–25.78)	0.001	5.94 (1.08–32.53)	0.040	7.63 (2.05–28.41)	0.002
Time from birth to HR increase >100BPM (s)	1.003 (0.99–1.00)	0.13	1.002 (0.99–1.01)	0.44		
Time to achieve 6 ml/kg (s)	1.00 (0.99–1.01)	0.18	1.00 (0.98–1.02)	0.97		
Mask leak (%)	0.98 (0.97–0.99)	0.026	0.98 (0.96–1.01)	0.37		
Median time of PPV (s)	1.002 (1.001–1.003)	<0.001	1.001 (1.00–1.002)	0.15	1.002 (1.001–1.003)	0.001
No ventilation before 6 ml/kg (s)	1.01 (0.99–1.02)	0.06	1.01 (0.98–1.03)	0.45		

PPV, positive pressure ventilation; FHRT, fetal heart rate; HR, heart rate; s, seconds; BPM, beats/minute; AOR, adjusted odds ratio; CI, confidence interval; LR, logistic regression.

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The findings that newborns who died were more likely to exhibit an abnormal FHRT pattern during labour, present with lower HR at the initiation of ventilation, remain with a HR <100 BPM at the end of ventilation, and require PPV for a longer period strongly supports the mechanism of intrapartum asphyxia (interruption of placental blood flow) as a major cause of these cardio-respiratory findings. Three reasons may account for the slower HR response to ventilation. First, the newborns may have been in secondary apnoea with profound acidemia and a stunned myocardium. Second, ventilation was performed with a self-inflating bag

Table 4. Logistic regression model for independent post-natal predictors of death within first 7 days among admitted newborns.

Variables	Univariable analysis OR (95% CI)	*P* value	Multivariable analysis with all variables into the model AOR (95% CI)	*P* value	Multivariable analysis after backward LR elimination AOR (95% CI)	*P* value
Admission temperature	0.49 (0.30–0.78)	0.003	0.64 (0.28–1.47)	0.29		
Oxygen saturation	0.97 (0.95–0.99)	0.003	0.99 (0.95–1.04)	0.68		
Blood glucose	1.13 (0.93–1.38)	0.20	1.26 (0.88–1.8)	0.20		
Seizures	5.91 (2.28–15.3)	<0.001	3.00 (0.48–18.8)	0.24		
HIE						
Normal/Mild	1		1		1	
Moderate/severe	13.0 (4.74–39.40)	<0.001	10.5 (2.12–52.8)	0.004	13.0 (4.74–39.40)	<0.001

HIE, hypoxic ischaemic encephalopathy; AOR, adjusted odds ratio; CI, confidence interval; LR, logistic regression.

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without PEEP, which may have limited the ability to establish FRC; the latter has been shown to be intimately related to an increase in HR [12]. Third, quality of PPV may have been inadequate as there was a significant delay in achieving a targeted V_t of 6 ml/kg in newborns who died, likely contributed to by low lung compliance of newborns in secondary apnoea.

Several factors may have contributed to the quality of delivered inflations. First, Skare et al. noted that 50 percent of ventilated newborns had a ventilation fraction of 60% during the first 30 seconds of ventilation, indicating interruption rather than continuous PPV [23]. Newborns in our study had a similarly low ventilation fraction of 66% during first 60 seconds. This is inconsistent with current HBB guidelines, which recommend uninterrupted ventilation until spontaneous breathing begins [18]. Interruptions of PPV may result in derecruitment and may have contributed to further delays in achieving FRC. Furthermore, the delay in initiating PPV was well beyond the recommended time of within 60s after birth, termed the "Golden Minute" [18]. We have reported previously that for every 30-second delay in initiating ventilation, there is a 16% increased risk of death [2]. Although the delay in initiating ventilation was comparable in both groups, it may still have influenced the time to establish FRC. Second, the inadequate volume that was delivered during the first 60s, coupled with the increased number of ventilations needed to achieve a desired goal of 6 ml/kg, likely led to prolonged time to establish FRC in the newborns who died [12]. Whether this reflects the use of a self-inflating bag without PEEP, or relates to ventilation technique remains unclear. Third, mask leak was substantial (range of 40 to 50%) in both groups although less in those who died versus survivors. However, despite the interrupted PPV and significant mask leakage, newborns were still able to receive adequate V_t during the whole episode of PPV. This finding concurs with other human and mannequin studies indicating that despite mask leak, delivered tidal volume is unaffected [10,24,25]. Interestingly, as noted above, newborns who died had less mask leakage as compared to survivors. We speculate that the prolonged PPV among the babies who died may have resulted in improvement of ventilation technique and less mask leak over time. Despite all these factors that may have contributed to a poorer quality, PPV was not a significant predictor of death in the final analytical model.

Moderate/severe HIE was the most important postnatal predictor of death. The findings of an abnormal FHRT, immediate bradycardia upon delivery, and the more sustained bradycardia with PPV, strongly supports the interruption of placental blood flow as the proximate cause of the brain injury. To our knowledge, this is the first time that intrapartum events have been closely linked to early severe encephalopathy in a resource-limited setting. An additional factor that may have contributed to the severe brain injury was the hypothermia noted at the time of admission to the newborn area. This may have affected cardiac function and brain perfusion. Hypothermia also decreases cerebral metabolic rate, which, in turn, reduces cerebral utilization of glucose.

Hypothermia has been shown to increase mortality in newborns, and in particular those of low birth weight, possibly through its well-described negative effects on respiratory function, i.e., inhibiting the action of surfactant, and an increased risk of sepsis [26]. Furthermore, hypothermia in the context of associated birth asphyxia has been reported to increase the risk of death in a dose-dependent manner [27,28]. This is in contrast to the neuro-protective role of controlled therapeutic hypothermia in the management of newborns with encephalopathy in resource-replete countries [29]. Nevertheless, interpretation of the findings regarding hypothermia in this study should be done cautiously due to significant missing data.

This study was carried out in a typical rural hospital with many neonatal deaths due to birth asphyxia. The ability to measure and rapidly detect the HR during PPV and link it to events that occurred before birth is a major strength of this study. In addition, we were able to study a group of high-risk asphyxiated newborns, and to document the HR responses to PPV.

The limitations of this study include the possibility that gaseous exchange did not take place in some neonates, despite the finding of adequate expired volume. In addition, all ventilations were performed without PEEP, which could in part explain the delayed observed HR response. Furthermore, we had significant missing data on some of the variables. Finally, it is also important to acknowledge that the newborns who died in this low-resource setting may have survived without neurologic injury in a setting where advanced newborn care is available.

Conclusion

This study showed that newborns depressed at birth with bradycardia, and with subsequent progression to death, had significantly delayed HR response to PPV as compared to survivors. Newborns who exhibited delayed HR response were also observed to have abnormal FHRT patterns, low Apgar scores and bradycardia at birth, likely related to intrapartum asphyxia. These infants went on to present with moderate/severe encephalopathy and seizures, the former being a significant predictor of death. Although the quality of PPV was not a significant predictor of death in the final analysis, it could have influenced outcome through delayed establishment of FRC. Finally, measures to improve FHRT monitoring during labour, and identification of those fetuses at high risk of severe brain injury, might help to decrease mortality due to perinatal asphyxia in the resource-limited setting.

Supporting information

S1 Data File.
(SAV)

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References

1. UNICEF, WHO. Levels & Trends in Child Mortality. Rep 2015. 2015;1–34.
2. Ersdal HL, Mduma E, Svensen E, Perlman JM. Early initiation of basic resuscitation interventions including face mask ventilation may reduce birth asphyxia related mortality in low-income countries. A prospective descriptive observational study. Resuscitation. 2012; 83(7):869–873. https://doi.org/10.1016/j.resuscitation.2011.12.011 PMID: 22198423
3. Hooper SB, Te Pas AB, Lewis RA, Morley CJ. Establishing Functional Residual Capacity at Birth. Neoreviews. 2010; 11(9):e474–483.
4. Palme-Kilander C, Tunell R. Pulmonary gas exchange during facemask ventilation immediately after birth. Arch Dis Child. 1993; 68(1 Spec No):11–16. PMID: 8439189

5. Perlman JM, Risser R. Cardiopulmonary Delivery. Arch Pediatr Adolesc Med. 1995; 149:20–25. PMID: 7827654
6. Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Vol. 132, Circulation. 2015. 2015; 132(suppl 1):S204–S241.
7. Mian QN, Pichler G, Binder C, O'Reilly M, Aziz K, Urlesberger B, et al. Tidal volumes in spontaneously breathing preterm infants supported with continuous positive airway pressure. J Pediatr. 2014; 165 (4):702–706. https://doi.org/10.1016/j.jpeds.2014.06.047 PMID: 25070013
8. Mortola JP, Fisher JT, Smith JB, Fox GS, Weeks S, Willis D. Onset of respiration in infants delivered by cesarean section. J Appl Physiol. 1982; 52(3):716–724. https://doi.org/10.1152/jappl.1982.52.3.716 PMID: 7068487
9. Te Pas AB, Wong C, Kamlin COF, Dawson JA, Morley CJ, Davis PG. Breathing Patterns in Preterm and Term Infants Immediately. 2009; 65(3):352–356.
10. Schmölzer GM, Kamlin OCOF, O'Donnell CPF, Dawson JA, Morley CJ, Davis PG. Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed. 2010; 95(6):F393–397. https://doi.org/10.1136/adc.2009.174003 PMID: 20547584
11. Schilleman K, Van Der Pot CJM, Hooper SB, Lopriore E, Walther FJ, Te Pas AB. Evaluating manual inflations and breathing during mask ventilation in preterm infants at birth. J Pediatr. 2013; 162(3):457–63. https://doi.org/10.1016/j.jpeds.2012.09.036 PMID: 23102793
12. Linde JE, Schulz J, Perlman JM, Øymar K, Blacy L, Kidanto H, et al. The relation between given volume and heart rate during newborn resuscitation. Resuscitation. 2017; 117:80–86. https://doi.org/10.1016/j.resuscitation.2017.06.007 PMID: 28606716
13. Hooper SB, Fouras A, Siew ML, Wallace MJ, Kitchen MJ, Pas AB te, et al. Expired CO2 Levels Indicate Degree of Lung Aeration at Birth. PLoS One. 2013; 8(8):e70895 https://doi.org/10.1371/journal.pone.0070895 PMID: 23951032
14. Yam CH, Dawson JA, Schmölzer GM, Morley CJ, Davis PG. Heart rate changes during resuscitation of newly born infants <30 weeks gestation: an observational study. Arch Dis Child Fetal Neonatal Ed. 2011; 96(2):F102–7. https://doi.org/10.1136/adc.2009.180950 PMID: 21126997
15. Ersdal HL, Eilevstjønn J, Linde JE, Yeconia A, Mduma ER, Kidanto H, et al. Fresh stillborn and severely asphyxiated neonates share a common hypoxic-ischemic pathway. International Journal of Gynecology and Obstetrics. 2018; 141(2):171–180 https://doi.org/10.1002/ijgo.12430 PMID: 29250782
16. Kasdorf E, Perlman JM. Strategies to prevent reperfusion injury to the brain following intrapartum hypoxia-ischemia. Semin Fetal Neonatal Med. 2013; 18(6):379–384. https://doi.org/10.1016/j.siny.2013.08.004 PMID: 24035475
17. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury. J Pediatr. 2009; 155(3):318–323. https://doi.org/10.1016/j.jpeds.2009.03.040 PMID: 19540512
18. The American Academy of of Pediatrics. Helping Babies Breathe. 2009. Available from: https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/Helping-Babies-Breathe.aspx
19. Linde JE, Schulz J, Perlman JM, Øymar K, Francis F, Eilevstjønn J, et al. Normal Newborn Heart Rate in the First Five Minutes of Life Assessed by Dry-Electrode Electrocardiography. Neonatology. 2016; 110(3):231–237. https://doi.org/10.1159/000445930 PMID: 27250761
20. World Health Organization. Maternal, Newborn, Child and Adolescent Health. Essential newborn care. World Health Organization. 2010. Available from: http://www.who.int/maternal_child_adolescent/documents/newborncare_course/en/
21. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, et al. Controversies Regarding Definition of Neonatal Hypoglycemia: Suggested Operational Thresholds. Pediatrics. 2000; 105(5):1141–1145. PMID: 10790476
22. Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteno CD, et al. The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr. 1997; 86(7):757–761. PMID: 9240886
23. Skåre C, Boldingh A, Nakstad B, Calisch TE, Niles DE, Nadkarni VM, et al. Ventilation fraction during the first 30s of neonatal resuscitation. Resuscitation. 2016; 107:25–30. https://doi.org/10.1016/j.resuscitation.2016.07.231 PMID: 27496260
24. Thallinger M, Ersdal HL, Ombay C, Eilevstjønn J, Størdal K. Randomised comparison of two neonatal resuscitation bags in manikin ventilation. Arch Dis Child Fetal Neonatal Ed. 2016; 101(4):F299–303. https://doi.org/10.1136/archdischild-2015-308754 PMID: 26437670

25. O'Donnell CPF, Davis PG, Lau R, Dargaville P a, Doyle LW, Morley CJ. Neonatal resuscitation 2: an evaluation of manual ventilation devices and face masks. Arch Dis Child Fetal Neonatal Ed. 2005; 90 (5):F392–396. https://doi.org/10.1136/adc.2004.064691 PMID: 15871989

26. Laptook AR, Salhab W, Bhaskar B. Admission Temperature of Low Birth Weight Infants: Predictors and Associated Morbidities. Pediatrics. 2007; 119(3):e643–649. https://doi.org/10.1542/peds.2006-0943 PMID: 17296783

27. Mathur NB, Krishnamurthy S, Mishra TK. Evaluation of WHO classification of hypothermia in sick extramural neonates as predictor of fatality. J Trop Pediatr. 2005; 51(6):341–345. https://doi.org/10.1093/tropej/fmi049 PMID: 16014762

28. Mullany LC, Katz J, Khatry SK, LeClerq SC, Darmstadt GL, Tielsch JM. Neonatal hypothermia and associated risk factors among newborns of southern Nepal. BMC Med. 2010; 8:43. https://doi.org/10.1186/1741-7015-8-43 PMID: 20615216

29. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ. 2010; 340:c363–c363. https://doi.org/10.1136/bmj.c363 PMID: 20144981

Paper III

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Factors affecting effective ventilation during newborn resuscitation: a qualitative study among midwives in rural Tanzania

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ORIGINAL ARTICLE

Factors affecting effective ventilation during newborn resuscitation: a qualitative study among midwives in rural Tanzania

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ABSTRACT

Background: Intrapartum-related hypoxia accounts for 30% of neonatal deaths in Tanzania. This has led to the introduction and scaling-up of the Helping Babies Breathe (HBB) programme, which is a simulation-based learning programme in newborn resuscitation skills. Studies have documented ineffective ventilation of non-breathing newborns and the inability to follow the HBB algorithm among providers.

Objective: This study aimed at exploring barriers and facilitators to effective bag mask ventilation, an essential component of the HBB algorithm, during actual newborn resuscitation in rural Tanzania.

Methods: Eight midwives, each with more than one year's working experience in the labour ward, were interviewed individually at Haydom Lutheran Hospital, Tanzania. The audio recordings were transcribed and translated into English and analysed using qualitative content analysis.

Results: Midwives reported the ability to monitor labour properly, preparing resuscitation equipment before delivery, teamwork and frequent ventilation training as the most effective factors in improving actual ventilation practices and promoting the survival of newborns. They thought that their anxiety and fear due to stress of ventilating a non-breathing baby often led to poor resuscitation performance. Additionally, they experienced difficulties assessing the baby's condition and providing appropriate clinical responses to initial interventions at birth; hence, further necessary actions and timely initiation of ventilation were delayed.

Conclusions: Efforts should be focused on improving labour monitoring, birth preparedness and accurate assessment immediately after birth, to decrease intrapartum-related hypoxia. Midwives should be well prepared to treat a non-breathing baby through high-quality and frequent simulation training with an emphasis on teamwork training.

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Background

Of the 130 million babies born each year worldwide, three million will die within the first four weeks of life. The burden of neonatal mortality rests almost entirely on poor countries with an estimated one million newborn deaths occurring in Sub-Saharan Africa each year. Intrapartum-related hypoxia accounts for more than a quarter of these deaths, and contributes to an unknown number of disabilities [1,2].

The goal of early basic resuscitation of an apneic newborn is reversal of the hypoxic-ischemic process and, ultimately, initiation of spontaneous respirations. Accurate evaluation of heart rate and respiration, coupled with prompt initiation of basic resuscitation interventions is thought to be critical for successful neonatal outcome [3]. In 2009, the Tanzanian Ministry of Health, Community Development, Gender, Elderly and Children introduced a learning programme called Helping Babies Breathe (HBB) [4], to teach midwives basic newborn resuscitation to help reduce the burden of perinatal hypoxia. The initial evaluation, conducted at eight sites, showed a 47% reduction in early neonatal deaths within 24 hours, and a 24% reduction in fresh stillbirths [5]. Furthermore, the roll-out of HBB has helped to supply health facilities with important resuscitation equipment [6]. Haydom Lutheran Hospital (HLH) was one of the initial eight HBB sites, and several quantitative studies related to HBB have been conducted there [5,7–9]. In 2013, building on the HBB programme, a large research and innovation project named Safer Births started, and all delivery rooms at HLH were equipped with newborn resuscitation monitors (Laerdal Global Health). These monitors record various ventilation parameters, such as heartrate, expired volume,

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expired CO_2, and inspiratory pressure for research purposes; however, only heart rate is displayed on the monitor visible to the provider during resuscitation [10,11].

At HLH, frequent HBB simulation training was shown to improve clinical outcomes, indicating a successful transfer of new knowledge and skills into clinical practice [7]. However, several studies have identified problems during actual newborn resuscitation, including the inability to quickly identify a newborn who needs assistance, the inability to correctly identify and use the heart rate to guide decisions, delays in initiating BMV, and the inability to administer effective ventilation [8,12–14]. These studies recommended more training and research to increase insight on how to improve newborn resuscitation.

Alternatively, few qualitative studies have investigated the midwives' perspective on the challenges related to newborn resuscitation in low-income countries. A lack of equipment, inadequate skills and knowledge, and ineffective communication are among the factors reported to hinder effective resuscitation, while training and good education are thought to decrease newborn morbidity and mortality [15,16]. Because low-income countries contribute significantly to the burden of intrapartum asphyxia, there is a need to better understand the context-specific factors that affect effective ventilation within these regions.

The aim of this study was to explore factors affecting effective ventilation during newborn resuscitation. Specifically, the barriers and facilitators to BMV and midwives' experiences of using the newborn resuscitation monitor were explored. Because newborn ventilation is mainly performed by midwives in Tanzania, their thoughts, views and experiences will offer great insight on how ventilation practices can be improved in the future.

Methods

Study area and context

HLH is situated in Mbulu District of Manyara Region, northern Tanzania. The immediate catchment area covers a population of approximately 450,000. HLH has approximately 5000 deliveries annually, and midwives largely conduct all deliveries. Doctors do not attend all deliveries; however, they are on call 24 hours a day to attend emergencies, including caesarean section, when called upon. On admission, women are assessed by the intern doctors on call and a midwife. For high-risk pregnancies, and other obstetric complications during labour, an obstetrician is called to review the patient. Otherwise, midwives will continue with labour management using partograph until the baby is delivered. Basic resuscitation of the newborn is performed by the attending midwives with the help of nurse assistants. Due to the high turnover of hospital staff, not all midwives have undergone full HBB training; some have only participated in short resuscitation training sessions. All nurses who were interviewed held a diploma in nursing, which is a three-year training programme to become a registered nurse midwife (RNM).

Study design

This was a qualitative study where individual, semi-structured interviews with midwives were conducted and audio recorded using a digital audio recorder. The individual interview method was chosen because it provides insight into people's thoughts, feelings and behaviours on important and lifesaving issues such as resuscitation [17].

Sampling and sample size

Midwives who had worked in the labour ward for more than one year and who had conducted more than three newborn resuscitations during that time were eligible for selection. This ensured the inclusion of information-rich informants [18]. Participants were recruited until a saturation point was reached, where no more new information was extracted from the data [17,19,20].

Data collection

Interview sessions were conducted within the hospital premises, in a private office at the convenience of the participant. The first author conducted two initial interviews to finalise the interview guide. The interview guide had questions under the following headings: communication and cooperation during resuscitation; initiation of ventilation; continuation of ventilation; resuscitation training; resuscitation protocol; and resuscitation monitoring.

The rest of the interviews were conducted by one research assistant: a psychologist working at the hospital. He was introduced to the interview guide and then he conducted one pilot interview, which was approved by the rest of the research group. The interviews lasted an average of 40–50 minutes.

At the end of each interview day, RM together with one senior researcher in our group, reviewed the information that had been collected to generate an emerging understanding regarding newborn ventilation before the subsequent interview session. This iterative process of data collection and review was used to shape the questions being asked in the subsequent interviews, as well as to recognize the point at

which no new information emerged [21]. The interviews were conducted in Swahili.

Analysis

The audio recordings were transcribed and then translated into English for our English-speaking researchers. Each paragraph was translated and positioned below the original Swahili paragraph to preserve the meaning of the whole paragraph. The first author checked each transcription and translation to ensure its quality, and minor mistakes were corrected before analysis began. The interview transcripts were then read and re-read to identify text relevant to newborn ventilation. Qualitative content analysis [22] was preferred as the method of analysis because it allows for data to be interpreted and acted on for their meanings. Using this method, the text containing key thoughts about ventilation was then condensed, abstracted and labelled with a code. The codes were re-visited to remove text that was not relevant to our research question but also to avoid repetitions. We discussed the codes and grouped similar codes to obtain sub-categories, and similar sub-categories were grouped into categories (Table 1). RM, CKM and other members of the research team were responsible for sorting and obtaining categories using a constant comparative method [21]. NVivo 11 software was used to facilitate the generation and sorting of codes.

Results

Eight midwives, aged between 26 and 47 years with a median of 8 years of experience in the labour ward, were interviewed between December and January 2016. Each had performed at least 10 resuscitations in her career. The main categories identified that influence effective ventilation were: 1) proper monitoring of labour and preparation for delivery helps to start ventilation on time; 2) teamwork among midwives during resuscitation determines how quickly ventilation could be initiated; 3) increased frequency of training with improved manikins improved newborn ventilation; 4) challenges in assessing clinical responses delay the next course of action; and 5) anxiety and fear affect technique and performance of ventilation (Table 2).

Monitoring of labour and preparation for delivery help to start ventilation on time

Labour monitoring

Midwives mentioned the importance of close monitoring of labour for early detection of problems and preparedness for starting timely when necessary. They mentioned the importance of being aware of the possibilities of delivering a depressed baby in need of help. Good monitoring of labour was reported to be associated with a decreased need for resuscitation, but, if indicated, the health-care workers would be ready:

> Once we see a woman has been labouring for a long time, we get prepared to resuscitate the baby because we know anything can happen. If we are three of us, the one conducting delivery will continue to do so, another one will wear gloves and wait for the baby while the third one will be around ready to assist. This is when we see indications that the baby is tired. (RNM 4)

Preparation of equipment

Midwives reported that the preparation of equipment, and sometimes staff, for unforeseeable and foreseeable resuscitations, helps them to start ventilation on time, reduces anxiety and increases the chances of a baby surviving resuscitation. They reported the importance of storing equipment in a dedicated place and inspecting it before each delivery, making it readily available

Table 1. Illustration of how codes, sub-categories and categories were obtained.

Interview quote	Code	Sub-category	Category
What helps is the initial preparation, before any delivery we prepare our equipment making sure they function well. (RNM 2)	Preparation of equipment's before delivery	Preparation of equipment and staff	
For now it is not difficult since we have it in place, not like in the past where when the baby is born that's when you run to look for it 'guys can I have a mask, can I have this' (RNM 1)	Resuscitation equipment located in one place		
Sometimes it happens that you deliver another woman in the labour room that it's equipment has already been used without cleaning, it leads to delays in helping another baby (RNM 5)	Uncleaned equipment leads to delays starting ventilation		Proper monitoring of labour and preparation for delivery helps to start ventilation on time
First thing is to detect a baby who will need resuscitation during monitoring of labour, that the woman is going to deliver soon and there is abnormal foetal heart rate (RNM 2)	Monitoring of foetal heart rate during labour	Close monitoring of labour to detect problems early	
You will have doubts since she had prolonged second stage, and you wonder if the baby will come out OK, you will have to call for help because you don't know what will happen after delivery (RNM 3)	Prepared to do resuscitation after diagnosing foetal distress		

Table 2. Categories and sub-categories in order of their importance according to how many times it was mention by the midwives to affect ventilation.

Category in order of importance as reported by midwives	*Sub-category*
1. Increased frequency of training to improve newborn ventilation	*1. Increased frequency of self-practice to improve knowledge, skills and confidence during ventilation*
	2. Improving simulation training to prepare midwives for ventilation
2. Monitoring of labour and preparation for delivery help to start ventilation on time	*1. Preparation of equipment*
	2. Labour monitoring
3. Teamwork and commitment during resuscitation determine how quick ventilation can be initiated	*1. Cooperation*
	2. Non-caring attitude
4. Difficulties interpreting clinical responses delay subsequent actions during resuscitation	*Resuscitation monitor provides quick assessment without interrupting ventilation*
5. Anxiety and fear affect technique and ventilation performance	

when needed. This practice was adopted during the implementation of the monitors that include the bag and mask. These are mounted on the wall in front of the resuscitation table and it is easy to see if the bag is missing. Every morning, one dedicated person inspects whether the monitors and bag-mask are in place and functioning.

> I get prepared once I suspect that the newborn will not breathe, therefore, I check my equipment, and if they are not well prepared, I will prepare them for resuscitation. (RNM 5)

Poor preparation or misplaced equipment was said to lead to delays in starting ventilation, by wasting time having to look for it. Midwives reported a situation where some of the used equipment, such as bags and masks, were found to be dirty at a time when they were needed urgently.

Teamwork and commitment during resuscitation determine how quickly ventilation could be initiated

Cooperation

According to the midwives, resuscitation is performed more effectively by two or more midwives helping each other. One midwife will ventilate the baby, while the others will be watching and monitoring the actions of the rescuer. Although the number of midwives at the hospital does not allow them to work in pairs at all times, they do call each other for assistance prior to delivery. Being with a colleague during delivery was reported to be important even if there were no anticipated problems:

> I normally don't allow myself to deliver a woman when I am alone, I will always call my colleague to be around no matter how busy they are, even if I see no indications that I will encounter problems, because you never know what will happen. (RNM 4)

Working together as a team enables midwives to use each other's strengths when they are faced with difficulties. In the presence of colleagues, midwives can communicate ways of improving on-going resuscitation, such as covering the baby to maintain warmth or alerting the person ventilating to adjust the face-mask to obtain a better mask seal should they note poor chest-rise. In other circumstances, midwives who are observing the resuscitation might take over the ventilation if they think their colleague is struggling to ventilate. One midwife commented;

> That is a possibility [taking over ventilation], once you see that she is not managing to get air in, then you ask to help her, and what we care about is the life of the baby, therefore you can't keep quiet, you ask her to let another person ventilate. (RNM 3)

Alternatively, midwives shared their experiences of not being organized, leading to confusion, interference and interruptions in ventilation when resuscitation is attended by more than two midwives. They reported that it is not routine to agree on the role for each midwife during resuscitation, especially when resuscitation was not anticipated. However, one midwife will always be prepared to receive the baby after the cord has been separated.

> Sometimes I might cover the baby but left the chest uncovered so that I see if I am getting air in, but another person will only think that I am exposing the baby therefore will come and cover the baby. Sometimes when there are many of us it is not good. (RNM 6)

Non-caring attitude

It was reported by the midwives that a few of their colleagues had questionable attitude and drive when saving lives during labour and delivery because of the way they respond to emergencies. This, in turn, can slow down their response to a non-breathing baby when a colleague is in need of help and hence delay the initiation of ventilation:

> There is this attitude or behaviour of not caring, you might find your colleague has no patient in her delivery room and you happen to have an emergency like you have delivered an asphyxiated baby in your room, you call her to come and help, and she comes very slowly, like it's not an emergency or like she doesn't want to help. (RNM 2)

When one midwife was questioned about whether she or other health care workers have tried to confront midwives with such attitude, she responded that they do not take any action in order to maintain a

social relationship, especially outside the working environment.

Lack of joint decision-making between midwives and doctors

It was further reported that sometimes the opinions of midwives are not taken into consideration when doctors make decisions about women in labour. This lack of collaboration between doctors and midwives stems from the fact that doctors have the final decision, and midwives are left without an option, only to document what they have done or what they have been advised to do. Midwives felt that this adds to the burden of babies who need to be ventilated unnecessarily. One midwife recounted a previous event:

> I told the doctor that it would be difficult to deliver this baby, but he reviewed and examined the mother, and he said she would deliver. Later I told the doctor you will not leave until we have delivered this baby, and once the baby came out we had to resuscitate for a long time but later the baby died. (RNM 4)

Increased frequency of training to improve newborn ventilation

Increased frequency of self-practice to improve knowledge, skills and confidence during ventilation

Midwives suggested that the only way to improve their performance is through increased training frequency and repeated self-practice to acquire the techniques and skills necessary for performing resuscitation. It was pointed out that the HBB programme helped them to increase their perceived confidence during resuscitation, although it took them some time before they were comfortable with the algorithm:

> When you see a baby is flat after initial drying, you start to call for help, then you try to perform suctioning without knowing where to start, from the mouth or nose, sometimes you even cut the cord before stimulation and you start bagging before even suctioning, in-short, we used to panic. But later, when we continued to practice we came to understand step after step, where to start and proceed until the end. (RNM 2)

Midwives agree that ventilation skills take time and practice to be acquired. They also mentioned a variation in levels of knowledge and skills between midwives, which contributes to increased interruptions during ventilation and delays in starting ventilation. Interrupting ventilation was thought to be due to a lack of knowledge about its consequences.

Ventilation practice used to take place twice weekly after the morning report for some time at Haydom Hospital. However, that practice was stopped after the person who initiated it left the hospital. Midwives thought it was a very good idea, as, during the sessions, there would be a supervisor watching them while they practiced, and it was an opportunity for them to be corrected if there was a certain skill they were not doing correctly. There was a suggestion from one midwife that the practical training should be followed by supervision during the actual resuscitation of babies in the labour ward:

> Maybe, during training, supervisors should be with us in the labour ward to witness two or three actual resuscitations so that they can continue to correct us whenever we do something wrong, because we will be doing it on real babies and not manikins. (RNM 4)

Improving simulation training to prepare midwives for ventilation

Midwives pointed out that the current skills training is not sufficient to prepare the midwives for actual resuscitation in the labour ward. The sense of urgency is missing. In addition, the manikins do not respond in any way when some of the interventions are performed on it:

> If there was a way of improving the manikin so that when we are stimulating there is something that shows you some improvement, like right now when you stimulate the manikin, nothing happens. (RNM 2)

Difficulties interpreting clinical responses delay subsequent actions during resuscitation

Immediately after delivery, midwives are supposed to quickly assess the newborn to determine whether it needs stimulation, suctioning and/or ventilation. Midwives mentioned a number of clinical signs that they look for to determine the next course of action. Such signs include whether the baby is breathing, its colour and activity, as well as its heart rate.

Midwives reported that failure to recognize early signs that a baby needs ventilation leads to a delay in starting ventilation, as they will be busy stimulating or suctioning:

> After stimulation and suction, sometimes you can see the baby responding, therefore you wait, but as you continue to wait, you see the colour starts to change and the breathing continues to be abnormal, but you have already wasted some time when you thought the baby would come up. (RNM 1)

Resuscitation monitor provides quick assessment without interrupting ventilation

Conversely, midwives reported that the resuscitation monitors help them to quickly determine the newborn's heart rate once there is a need to start ventilation. The monitor was reported to quickly provide heart rate as feedback during ongoing ventilation, as opposed to interrupting ventilation for auscultation (which was necessary in the past).

> But those monitors help, after initial stabilization, instead of using the stethoscope, you just attach the sensor, and you see on the screen the heart rate, therefore it makes things easy. (RNM 5)

Alternatively, midwives reported incidences when the monitor was not functioning in one of the labour rooms, making it necessary to move the baby to another room for resuscitation, which led to the loss of precious time for resuscitation.

Anxiety and fear affect technique and ventilation performance

Midwives reported that they sometimes became anxious once they realize that a baby is depressed. The fear and/or anxiety was reported to arise because of the pressure they feel to ensure the baby survives. When there is a possibility that the baby might not survive, or when the baby does not respond after a period of ventilation, the fear may turn to panic:

> … you become fearful thinking whether you will be able to save that life … that is why sometimes we panic. (RNM 4)

The fear/anxiety was reported to affect the way they ventilate the baby, such as the technique of holding the bag and mask, interrupting ventilation and skipping some steps of the guidelines. Additionally, fear was reported to be responsible for time loss during resuscitation:

> Once you have fear, you will not be able to hold it properly (the bag and mask) the way we have been instructed to, and you will get air leaks because you are shaking, you have fear, and the baby will not get the air you are giving it. (RNM 1)

Discussion

This study highlights the main facilitators and barriers currently facing Tanzanian midwives in their daily practice while attempting to rescue non-breathing babies at birth. Midwives' teamwork during resuscitation was mentioned as being an important factor in facilitating ventilation. Participants were clearly happy to help each other perform certain tasks once they were summoned. However, there was no pre-arrangement of the roles for each of the team members, leading to confusion or interference, and the exchange of roles during the actual intervention.

The lack of pre-arranged roles stems from the fact that HBB training is tailored to resource-limited settings where, mostly, resuscitation is performed by a single rescuer. Simmons et al. reported the importance of having clear roles and responsibilities during emergency and stressful interventions as being critical for positive outcomes [23]. Jordanian midwives reported lack of teamwork as a barrier to successful neonatal resuscitation [15]. All the nurses had received HBB training, which does not have a component for team-training. We therefore think it is important to consider teamwork during simulation training so that midwives can practise their roles and responsibilities in the delivery room.

A lack of joint decision-making between midwives and doctors has been reported previously in Tanzania [24]. Midwives and doctors frequently disagree on the management of patients, such as the decision to perform caesarean section [24]. In this study, midwives thought that sometimes their opinions were being ignored, despite their perceived clinical experience. Such conflicts might not seem to affect ventilation directly, but may affect team spirit, respect, confidence and communication between providers, and, subsequently, affect care and the outcome of some deliveries. It is therefore important for the management of health facilities to create an environment in which both midwives and doctors can work in harmony and with good understanding. This can be achieved by providing joint clinical obstetric training for both doctors and midwives.

Some midwives were reported as having a non-caring attitude when saving newborns during resuscitation. Although this comment was directed at only a few individuals, other studies in Tanzania and Kenya have highlighted similar issues, such as midwives' lack of motivation due to poor working conditions, and the feeling of not being recognized by their supervisors [25–28]. Motivating health-care workers in resource-poor settings can sometimes be a challenge. Nevertheless, supportive leadership and effective management at hospital level has been shown to modify the impact of resource shortfalls and foster good working relations between cadres [26,29].

The importance of appropriate labour monitoring, together with the preparation of resuscitation equipment, was mentioned as the most effective way of facilitating resuscitation. The fact that labour monitoring was highlighed as a facilitator of ventilation probably reflects that a sub-standard labour monitoring practice is taking place in this low-resource setting [30–32]. The monitoring of labour is one of the important steps in ensuring good foetal outcome; therefore, efforts should be geared towards improving and standardising labour monitoring for the benefits of the fetus and the mother.

After the introduction of HBB, health-care facilities in Tanzania were equipped with basic resuscitation equipment, therefore, a lack of equipment was not mentioned as a barrier, as has been reported in other low-income countries [15,16]. The World Health Organization (WHO) recommends the preparation of delivery equipment and supplies,

including newborn resuscitation equipment, whenever delivery is anticipated [33]. This view was shared by the midwives, as they emphasized the importance of having equipment ready, to be able to initiate ventilation within the first minute. Although the outcomes of resuscitation attempts depend on many things, such as the skillful use of resuscitation equipment, it is still vital to ensure that equipment is ready whenever it is needed.

Previous studies have reported the importance of frequent simulation training, as opposed to a single training session. Single training sessions have been associated with adequate skills retention [9,34]; however, frequent brief on-site sessions were shown to retain skills as well as improve the clinical outcomes of resuscitated babies [6]. Midwives reported that more practical training would increase their knowledge, skills, competence and confidence in performing ventilation. They went further to suggest that offering short training sessions during working hours, as opposed to self-practice alone, would make a difference in terms of outcome. A preference for more realistic simulation training was also brought up during the interviews. All of the midwives in this study had only received basic resuscitation training using the NeoNatalie (Laerdal Global Health) newborn manikin, which is a low-fidelity manikin. Simulation has many advantages, and results in highly trained health-care workers who are less likely to make life-threatening or costly medical errors [35].With adequate training, midwives will be able to respond quickly and efficiently to the needs of asphyxiated babies. Many high-income countries have already established advanced simulation training centres, a resource which also needs to be established in low-income countries. Furthermore, the introduction of debriefings as a learning tool during simulations, as well as after a serious clinical event, will help improve performance. Debriefing is a process in which people who have had a certain experience are led through a purposive discussion regarding the experience [36,37]. Unlike audits, debriefing helps the providers to learn and reflect on what they have experienced immediately after an actual or a simulated event, giving them a chance to learn from their experience.

Although the clinical signs used to assess newborns immediately after delivery are well known (Apgar: colour, tone, heart rate, respirations and reflexes), still there seems to be challenges in assessing a newborn baby correctly, which contributes to delays in instituting treatment or interventions. The Apgar score has been accepted for many years as a standard tool for the assessment of newborns immediately after delivery, despite being subjective and unreliable [38,39]. This study suggests that incorrect assessment and interpretation of the clinical signs are delaying the initiation of ventilation or influencing interruptions during ventilation. One way to improve this practice is through advanced simulation training, where dynamic, complex and unanticipated situations could be practised and managed. Midwives furthermore reported the usefulness of the resuscitation monitor to quickly determine the initial heart rate and heart rate responses to interventions; there is no need to auscultate for heart rate, avoiding unnecessary ventilation pauses. Midwives reported that displaying the time is crucial for them to keep track and see how many minutes have elapsed since resuscitation started. The monitor, when used properly, can help both in the initial assessment of the heart rate and as a feedback mechanism during actual ventilation.

Incidences of fear or anxiety when faced with a baby in need of ventilation came up during our discussions. Fear and anxiety was reported to affect ventilation performance and an inability to follow the HBB protocol during resuscitation. According to the midwives, fear or anxiety was a result of them feeling pressure to ensure that the baby survives. There could be a number of factors causing anxiety in these situations. Health-care workers may be questioned about perinatal deaths occurring during their shifts, especially if the mother had a live fetus during admission. One study, conducted in urban Tanzania, reported that midwives and doctors fear blame from peers or management during perinatal and maternal audits [24]. Furthermore, acute stressful medical situations tend to induce anxiety, which may affect performance, especially when health workers perceive themselves as not having enough resources to respond to the situation [40,41]. At HLH, maternal and perinatal audits do take place and this could be one of the contributing factors to the fear and anxiety. Audits are very important, but they need to be conducted in an appropriate and constructive manner, without naming, blaming or shaming health-care workers. Resuscitation training should have interventions geared towards improving performance under stress, or interventions for midwives to cope with and withstand stressors.

In this study, we ensured credibility by using midwives' narratives to describe their shared experiences in relation to newborn resuscitation. By using in-depth interviews, we believe we have chosen the best data collection method to address our objectives and confirm our credibility. Participants were selected carefully, considering their years of service as well as the number of resuscitations that they had. We included participants of various ages to increase variation. During analysis, we used qualitative content analysis, which allowed us to examine the text and make sense of it. We also ensured that all

relevant data were included in our categories by involving more than one researcher [22].

The use of an interview guide ensured consistency while keeping the sessions open enough for midwives to share their experiences. Initial interviews were used to modify the interview guide, and subsequent interviews took into consideration the information that was already collected, ensuring that we captured changes over time in data collection. Our participants were free to share their experiences during interviews due to the use of Swahili as the medium of communication. Our research group comprised midwives, paediatricians, obstetricians and anaesthesiologists, who brought with them extensive knowledge on newborn resuscitation, which helped to improve confirmability. Providing details about the context in which this study was carried out, as explained in detail in the methods section, together with quoted text in the results section, will help readers to compare these findings with their own context and decide the transferability of our findings.

Among the limitations of this study is our decision not to interview doctors who also work with nurses during labour and delivery. We made this decision because we thought that their contribution to the subject of newborn resuscitation would be limited, as they normally do not participate in resuscitations. Furthermore, we acknowledge the inclusion of midwives from only one rural hospital in Tanzania. Interviewing midwives from another facility in an urban area could have provided more insights and thus enriched our discussion.

Conclusion and recommendations

We have identified the ability to monitor labour properly, preparing resuscitation equipment before delivery, teamwork and frequent ventilation training as factors that facilitate effective ventilation. Barriers to effective ventilation were mentioned as being anxiety and/or fear during ventilation, and difficulties in assessing clinical responses during ventilation.

To improve the outcomes of resuscitated babies, we need skilled midwives who are competent and comfortable in resuscitation skills, including appropriate assessment of the newborn's condition immediately after delivery. Continued efforts are needed to improve simulation training through the use of more realistic manikins as well as increased frequency of practice. We have highlighted the importance of joint decision-making between midwives and doctors: it is high time that teamwork organization is introduced during resuscitation training in low-income countries.

Future studies on resuscitation in low-resource countries should focus on the best ways to improve training, including incorporating teamwork training, in an environment with a scarcity of health-care workers.

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Author contributions

All authors contributed in the designing of the study, the analysis, and the writing of the manuscript. They all approved the final version of the manuscript

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics and consent

Informed written consent was obtained from the participants after permission to conduct the study was granted by HLH administration and the National Institute of Medical Research in Tanzania.

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Paper context

Improving newborn resuscitation in low-income countries is critical to newborn survival. This study explored the views of midwives on how to improve newborn resuscitation. Midwives reported simple measures such as simulation training, preparation of equipment pre-delivery, labour monitoring and accurate assessment at birth to be equally important for resuscitation outcome. Fear, anxiety and the lack of team-training led to confusion and misunderstandings during resuscitation. This implies that resuscitation training should focus more on adequate preparation and team-training.

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References

[1] Lawn JE, Cousens S, Zupan J. 4 Million neonatal deaths: when? Where? Why? Lancet. 2005;365:891–900.

[2] UNICEF, WHO. Levels & trends in child mortality. Rep. 2015;2015:1–34.

[3] Perlman JM, Wyllie J, Kattwinkel J, et al. Part 7: neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation. 2015;132:204–241.

[4] American Academy of Paediatrics. Helping Babies Breathe. 2009 [cited 2017 Sept 22]. Available from: https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/default.aspx.

[5] Msemo G, Massawe A, Mmbando D, et al. Newborn mortality and fresh stillbirth rates in Tanzania after helping babies breathe training. Pediatrics. 2013;131:353–360.

[6] Arlington L, Kairuki AK, Isangula KG, et al. Implementation of "Helping Babies Breathe": A 3-year experience in Tanzania. Pediatrics. 2017;139:2016–2132.

[7] Mduma E, Ersdal H, Svensen E, et al. Frequent brief on-site simulation training and reduction in 24-h neonatal mortality-An educational intervention study. Resuscitation. 2015;93:1–7.

[8] Ersdal HL, Mduma E, Svensen E, et al. Early initiation of basic resuscitation interventions including face mask ventilation may reduce birth asphyxia related mortality in low-income countries. A prospective descriptive observational study. Resuscitation. 2012;83:869–873.

[9] Ersdal HL, Vossius C, Bayo E, et al. A one-day "Helping Babies Breathe" course improves simulated performance but not clinical management of neonates. Resuscitation. 2013;84:1422–1427.

[10] Linde JE, Schulz J, Perlman JM, et al. Normal newborn heart rate in the first five minutes of life assessed by dry-electrode electrocardiography. Neonatology. 2016;110:231–237.

[11] Linde JE, Schulz J, Perlman JM, et al. The relation between given volume and heart rate during newborn resuscitation. Resuscitation. 2017;117:80–86.

[12] Chitkara R, Rajani AK, Oehlert JW, et al. The accuracy of human senses in the detection of neonatal heart rate during standardized simulated resuscitation: implications for delivery of care, training and technology design. Resuscitation. 2013;84:369–372.

[13] Lindbäck C, Kc A, Wrammert J, et al. Poor adherence to neonatal resuscitation guidelines exposed; an observational study using camera surveillance at a tertiary hospital in Nepal. BMC Pediatr. 2014;14:233.

[14] Boon W, McAllister J, Attar MA, et al. Evaluation of heart rate assessment timing, communication, accuracy, and clinical decision-making during high fidelity simulation of neonatal resuscitation. Int J Pediatr. 2014;2014:927430.

[15] Kassab M, Alnuaimi K, Mohammad K, et al. Midwives experiences, education, and support needs regarding basic newborn resuscitation in Jordan. Clin Nurs Res. 2016;25:291–309.

[16] Bream KDW, Gennaro S, Kafulafula U, et al. Barriers to and facilitators for newborn resuscitation in Malawi, Africa. J Midwifery Women's Heal. 2005;50:329–334.

[17] Green J, Thorogood N. Qualitative methods for health research. 2nd ed. London: Sage Publications; 2009.

[18] Kuzel AJ. Sampling in qualitative inquiry: doing qualitative research. Thousand Oaks, CA: Sage Publications; 1992.

[19] Morse JM. The significance of saturation. Qual Health Res. 1995;5:147–149.

[20] Patton MQ. Qualitative research & evaluation methods. 3rd ed. Los Angeles: Sage Publications; 2002.

[21] Barbour R. Introducing qualitative research: a student guide to the craft of doing qualitative research. Los Angeles: Sage Publications; 2008.

[22] Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today. 2004;24:105–112.

[23] Simmons D, Sherwood G. Neonatal intensive care unit and emergency department nurses' descriptions of working together: building team relationships to improve safety. Crit Care Nurs Clin North Am. 2010;22:253–260.

[24] Litorp H, Mgaya A, Mbekenga CK, et al. Fear, blame and transparency: obstetric caregivers' rationales for high caesarean section rates in a low-resource setting. Soc Sci Med. 2015;143:232–240.

[25] Mselle LT, Moland KM, Mvungi A, et al. Why give birth in health facility? Users' and providers' accounts of poor quality of birth care in Tanzania. BMC Health Serv Res. 2013;13:174.

[26] Mbindyo P, Gilson L, Blaauw D, et al. Contextual influences on health worker motivation in district hospitals in Kenya. Implement Sci. 2009;4:43.

[27] Mselle LT, Kohi TW, Mvungi A, et al. Waiting for attention and care: birthing accounts of women in rural Tanzania who developed obstetric fistula as an outcome of labour. BMC Pregnancy Childbirth. 2011;11:75.

[28] Mahiti GR, Mkoka DA, Kiwara AD, et al. Women's perceptions of antenatal, delivery, and postpartum services in rural Tanzania. Glob Health Action. 2015;8:28567.

[29] Maaløe N, Housseine N, Bygbjerg IC, et al. Stillbirths and quality of care during labour at the low resource referral hospital of Zanzibar: a case-control study. BMC Pregnancy Childbirth. 2016;16:351.

[30] Pattinson RC. Challenges in saving babies - Avoidable factors, missed opportunities and substandard care in perinatal deaths in South Africa. South African Med J. 2003;93:450–455.

[31] Gans-Lartey F, O'Brien BA, Gyekye FO, et al. The relationship between the use of the partograph and birth outcomes at Korle-Bu teaching hospital. Midwifery. 2013;29:461–467.

[32] Lewis D, Downe S, FIGO Intrapartum Fetal Monitoring Expert Consensus Panel. FIGO consensus guidelines on intrapartum fetal monitoring: intermittent auscultation. Int J Gynaecol Obstet. 2015;131:9–12.

[33] WHO. Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice. Geneva: World Health Organisation; 2015.

[34] Arabi AME, Ibrahim SA, Ahmed SE, et al. Skills retention in Sudanese village midwives 1 year

following Helping Babies Breathe training. Arch Dis Child. 2016;101:439–442.
[35] Al-Elq AH. Simulation-based medical teaching and learning. J Family Community Med. 2010;17:35–40.
[36] Issenberg SB, Mcgaghie WC, Petrusa ER, et al. Features and uses of high-fidelity medical simulations that lead to effective learning : a BEME systematic review. Med Teach. 2005;1:10–28.
[37] Cho SJ. Debriefing in pediatrics. Korean J Pediatrics. 2015;58:47–51.
[38] American Academy of Pediatrics, Committee on Fetus and Newborn; American College of Obstetricians and Gynecologists and Committee on Obstetric Practice. The Apgar score. Pediatrics. 2006;117:1444–1447.
[39] Committee on Fetus and Newborn, American Academy of Pediatrics, and Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Use and Abuse of the Apgar score. Pediatrics. 1996;98:141–142.
[40] LeBlanc VR. The effects of acute stress on performance: implications for health professions education. Acad Med. 2009;84:S25–33.
[41] Hunziker S, Laschinger L, Portmann-Schwarz S, et al. Perceived stress and team performance during a simulated resuscitation. Intensive Care Med. 2011;37:1473–1479.