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Neonatal Resuscitation

Understanding challenges and identifying a strategy for implementation in Nepal

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Dissertation presented at Uppsala University to be publicly examined in Museum Gustavianum, Akademigatan 3, Uppsala, Wednesday, 10 February 2016 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Susan Niermeyer (Section of Neonatalogy, School Of Medicine, University of Colorado).

Abstract
KC, A. 2016. Neonatal Resuscitation. Understanding challenges and identifying a strategy for implementation in Nepal. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1166. 83 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-554-9434-6.

Despite the unprecedented improvement in child health in last 15 years, burden of stillbirth and neonatal death remain the key challenge in Nepal and the reduction of these deaths will be crucial for reaching the health targets for Sustainable development goal by 2030.

The aim of this thesis was to explore the risk factors for stillbirth and neonatal death and change in perinatal outcomes after the introduction of the Helping Babies Breathe Quality Improvement Cycle (HBB QIC) in Nepal.

This was a prospective cohort study with a nested case-control design completed in a tertiary hospital in Nepal. Information were collected from the women who had experienced perinatal death and live birth among referent population; a video recording was done in the neonatal resuscitation corner to collect information on the health workers' performance in neonatal resuscitation.

Lack of antenatal care had the highest association with antepartum stillbirth (aOR 4.2, 95% CI 3.2–5.4), births that had inadequate fetal heart rate monitoring were associated with intrapartum stillbirth (aOR 1.9, CI 95% 1.5–2.4), and babies who were born premature and small-for-gestational-age had the highest risk for neonatal death in the hospital (aOR 16.2, 95% CI 12.3–21.3). Before the introduction of the HBB QIC, health workers displayed poor adherence to the neonatal resuscitation protocol. After the introduction of HBB QIC, the health workers demonstrated improvement in their neonatal resuscitation skills and these were retained until six months after training. Daily bag-and-mask skill checks (RR 5.1 95% CI 1.9–13.5), preparation for birth (RR 2.4, 95% CI 1.0–5.6), self-evaluation checklists (RR 3.8, 95% CI 1.4–9.7) and weekly review and reflection meetings (RR 2.6, 95% CI 1.0–7.4) helped the health workers to retain their neonatal resuscitation skills. The health workers demonstrated improvement in ventilation of babies within one minute of birth and there was a reduction in intrapartum stillbirth (aOR 0.46, 95% CI 0.32–0.66) and first-day neonatal mortality (aOR 0.51, 95% CI 0.31–0.83).

The study provides information on challenges in reducing stillbirth and neonatal death in low income settings and provides a strategy to improve health workers adherence to neonatal resuscitation to reduce the mortality. The HBB QIC can be implemented in similar clinical settings to improve quality of care and survival in Nepal, but for primary care settings, the QIC need to be evaluated further.

Keywords: antepartum stillbirth, intrapartum stillbirth, neonatal mortality, first-day neonatal mortality, antenatal care, fetal heart rate monitoring, partogram, preterm, small-for-gestational-age, clinical adherence, neonatal resuscitation, skill retention, quality improvement cycle, Nepal

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Dedication to Rejina and Arshiya

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I.   Ashish KC, Nelin V, Wrammert J, Ewald U, Vitrakoti R, Baral GN, Malqvist M: **Risk factors for antepartum stillbirth: a case-control study in Nepal.** *BMC Pregnancy Childbirth*. 2015 Jul 5;15:146.

II. Ashish KC, Wrammert J, Nelin V, Ewald U, Clark R, Malqvist M: **Level of mortality risk for babies born preterm or with a small weight for gestation in a tertiary hospital of Nepal.** *BMC Public Health*. 2015 Sep 10;15(1):877.

III. Ashish KC, Wrammert J, Ewald U, Clark R, Gautam J, Baral GN, Baral KP, Malqvist M: **Incidence of intrapartum stillbirth and associated risk factors in tertiary care setting of Nepal: A case-control study.** Submitted

IV. Lindback C, Ashish KC, Wrammert J, Vitrakoti R, Ewald U, Malqvist M: **Poor adherence to neonatal resuscitation guidelines exposed; an observational study using camera surveillance at a tertiary hospital in Nepal.** *BMC pediatrics* 2014, 14:233.

V.   Ashish KC, Wrammert J, Nelin V, Ewald U, Clark R, Peterson S, Malqvist M: **Evaluation of Helping Babies Breathe Quality Improvement Cycle (HBB-QIC) on retention of neonatal resuscitation skills six month after training in a low-income setting like Nepal.** Submitted

VI. Ashish KC, Wrammert J, Clark R, Ewald U, Vitrakoti R, Pun A, Raaijmakers H, Malqvist M. **Reducing perinatal mortality in Nepal using Helping Babies Breathe.** *Pediatrics, accepted for publication.*

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Contents

Abbreviations

AGA	Appropriate-for-Gestational-Age
aOR	Adjusted Odds Ratio
APR	A Promise Renewed
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
cOR	Crude Odds Ratio
CCD	Charge Coupled Device
CSPro	Census and Survey Processing System
DMC	Data Monitoring Committee
ENAP	Every Newborn Action Plan
FHRM	Fetal Heart Rate Monitoring
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBB	Helping Babies Breathe
HW	Health Worker
ILCOR	International Liaison Committee on Resuscitation
IQR	Inter Quartile Range
KMC	Kangaroo Mother Care
LBW	Low Birth Weight
MDG	Millennium Development Goal
MNSC	Maternal and Newborn Service Center
NMR	Neonatal Mortality Rate
OSCE	Objective Structured Clinical Examination
QIC	Quality Improvement Cycle
QI	Quality Improvement
QIT	Quality Improvement Team
RR	Relative Risk
RDS	Respiratory Distress Syndrome
SBA	Skilled Birth Attendant
SD	Standard Deviation
SDG	Sustainable Development Goal
SFNRT	Standardised Formal Neonatal Resuscitation Training
SGA	Small-for-Gestational-Age
SPSS	Statistical Package for Social Science
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Glossary and definitions

Perinatal mortality	Deaths that occur during the perinatal period, including stillbirths of viable fetuses with gestational age beyond 22 weeks or birth weight more than 500 grams and neonatal deaths occurring within the first 7 days of life.
Stillbirth	Birth of a viable fetus with gestational age beyond 22 weeks or birth weight more than 500 grams, Apgar score of 0 at 1 and 5 minutes.
Antepartum stillbirth	Birth of a viable fetus with gestational age beyond 22 weeks or birth weight more than 500 grams, Apgar score of 0 at 1 and 5 minutes, signs of maceration, and no fetal heart sound at admission or at the onset of labor.
Intrapartum stillbirth	Birth of a viable fetus with gestational age beyond 22 weeks or birth weight more than 500 grams, Apgar score of 0 at 1 and 5 minutes, with no signs of maceration and who had fetal heart sound at admission and at the onset of labor.
First-day neonatal mortality	Death of a live-born infant within 24 hours of birth.
Early neonatal mortality	Death of baby between 0-6 days of birth.
Neonatal mortality	Death of an infant between 0-27 day of birth.
Parity	Number of times a woman has given birth after the age of viability, i.e. 22 weeks, including both live and still births[1].
Caste	The group within the social hierarchical system of Nepal to which the woman's family belongs [2].

Wealth index	The wealth index is a measure of socioeconomic position, used in nationally representative health surveys (Demographic Health Surveys) to compare socio-economic inequalities [3, 4]. During the interviews with mothers, data is collected on ownership of durable assets (e.g. car, refrigerator, bicycle, radio, television), housing characteristics (e.g. number of rooms, dwelling floor and roof materials, toilet facilities) and access to services (e.g. electricity supply, drinking water source). Using the scores from the first principal component analysis, a wealth index (asset index) is contructed. Based on the value of the index, individuals are sorted and established to create cut-off values for percentiles within the population. These quintiles are ranked from bottom to top as poorest, poorer, middle, richer and richest [5].
Antenatal care attendance	Whether a mother attended any antenatal care visits, during which she received clinical examination, counseling and medication (if needed) from a health worker.
Antepartum hemorrhage[6]	Vaginal bleeding before the onset of labor.
Hypertensive disorder of pregnancy [6]	Maternal diastolic blood pressure of 90 mmHg or more in two consecutive assessments, which are at least four hours apart, during pregnancy.
Medical complication during pregnancy[6]	Women having diabetes mellitus, severe anemia (Hemoglobin < 7 gm/dL), epilepsy, etc. during pregnancy.
Multiple pregnancy[6]	Woman pregnant with more than one fetus.
Hypertensive disorder during delivery [6]	Classified by maternal diastolic blood pressure greater than or equal to 90 mmHg in two separate recordings.
Mal-presentation [6]	When the fetus presented in any other position than the vertex presentation, i.e. with the top of the head first.

Prolonged labor [6]	When the cervix is not dilated beyond 4cm after eight hours of regular contractions or if cervical dilatation was to the right of the alert line on the partogram.
Prolapsed cord [6]	When the umbilical cord is present in the birth canal below the fetal presenting part or the umbilical cord is visible at the vagina following the rupture of membranes.
Gestational age of the infant	Gestational age measurement based on the mother's last menstrual period.
Birth weight	Weight of the baby measured within one hour of delivery using a weighing scale.
Small-for-gestational age	Babies with a birth weight below the tenth percentile for a given gestational age and sex, based on a standard optimal reference population [7].
Appropriate-for-gestational age	Babies with a birth weight between 10-90th percentile for a given gestational age and sex, based on a standard optimal reference population [7].
Preterm birth	Babies born before 37 completed weeks of gestation, estimated by the date of the mother's last menstrual period.
Term birth	Babies born at, or after, 37 completed weeks of gestation, estimated by the mother's last menstrual period.
Low Birth Weight (LBW)	Babies who weigh less than 2500 grams at the time of birth.

Introduction

Renewed global pledge for neonatal survival beyond 2015

Since the United Nations called for a reduction in child deaths through the announcement of Millennium Development Goal (MDG) 4 in 2001, there has been unprecedented investment in promoting child survival [8-10]. As a result of these efforts, there has been a reduction in the number of under-five deaths by more than half by 2015 [8-10]. Significant progress has also been made in the reduction of post-neonatal mortality; however, neonatal mortality reduction has been slow over the last 15 years. To further accelerate the rate of reduction of under-five deaths, there has been a global call for action to reduce the neonatal mortality rate to 10 or less per 1,000 live births and the stillbirth rate to 10 or less by 2035 in the form of the "Every Newborn Action Plan" [11, 12]. The Every Newborn Action Plan (ENAP) calls for priority actions to address preventable causes of neonatal mortality, that is to say, preterm birth complications, intrapartum-related complications, and infection [11, 13].

The 2015 UN General Assembly endorsed the seventeen Sustainable Development Goals for 2030 and one of the targets set is to: "by 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births" [14].

Burden of stillbirth and neonatal death

In 2010, globally, an estimated 5.5 million deaths of babies occurred between the third trimester pregnancy (stillbirth) and the first 28 days of birth (neonatal death) (Figure 1). Of the total 2.65 million stillbirths that occur every year, more than half (1.45 million) occurred during the antepartum period, while the remainder occurred during the intrapartum period [15, 16]. A reported 32% and 54% of antepartum and intrapartum stillbirths occurred in South Asia, respectively [16, 17]. In 2012, 2.9 million neonatal deaths

occurred globally and, of these, 35% took place during the first day of life, with 74% during first week of life (Figure 2). During the first week of life, 41% of the deaths were caused by complications due to preterm birth, 23% due to intrapartum-related complications, and 13% were related to infection (Figure 3) [17]. Identifying the risk factors for perinatal death and the implementation of evidence-based intervention are priority areas of research and action and will be crucial to reduce the burden of death [15, 18-20].
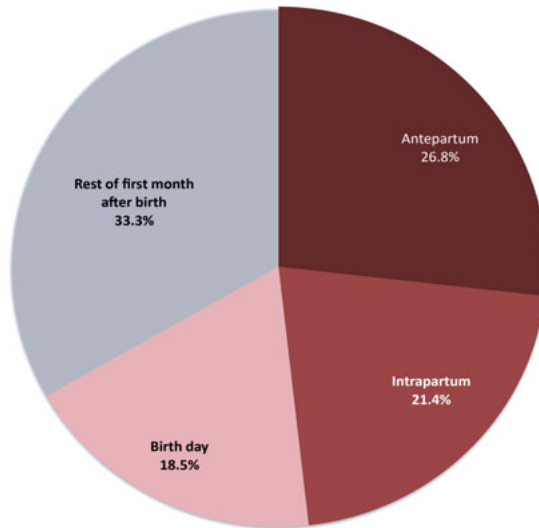

Figure 1. Proportion of mortality after third trimester of pregnancy (antepartum and intrapartum stillbirth) and until neonatal period (neonatal mortality) [17]
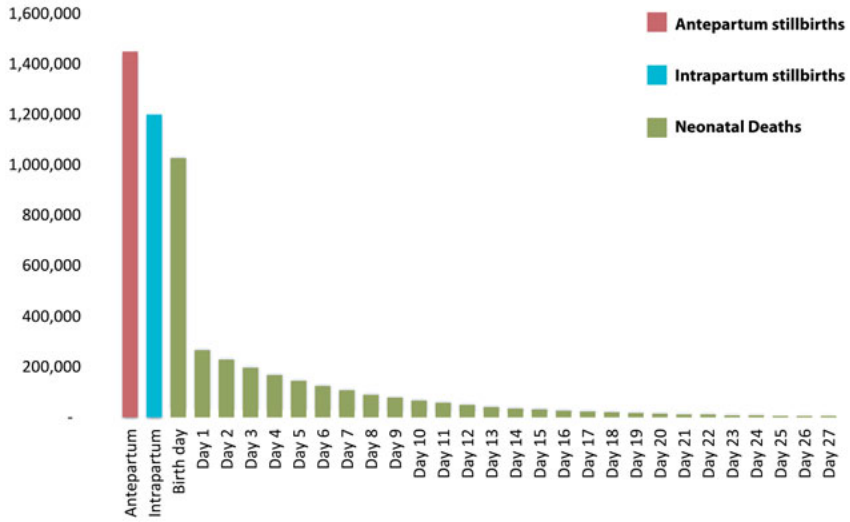
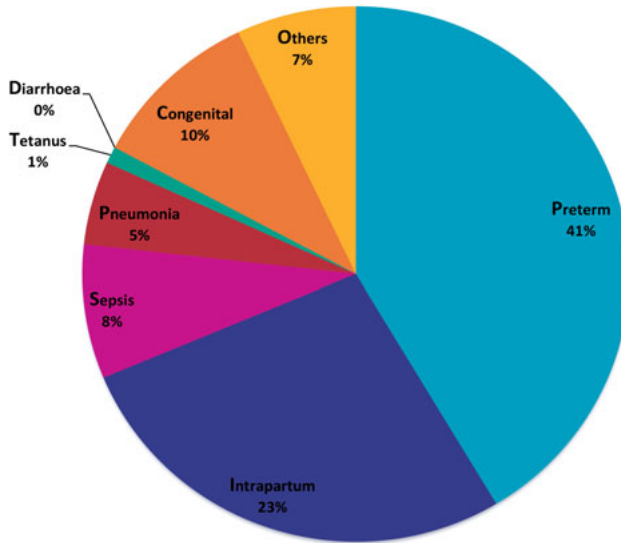*Figure 2. Timing of babies' deaths (third trimester stillbirth and neonatal death) [17]*

Figure 3. Causes of death during first seven days of life [17]

Risk factors for antepartum and intrapartum stillbirth

Maternal health is closely associated with newborn health, and there are a number of risk factors for poor maternal health that have been linked to poor fetal outcomes [21]. There are several risk factors identified as being associated with stillbirth in high-income countries; maternal age greater than 35 years, parity higher than four, low maternal educational status, lack of antenatal care attendance, chronic maternal medical conditions, preeclampsia or placenta abruption during pregnancy, intra-uterine growth restriction, major congenital anomaly of the infant, and poor maternal nutritional status [22-24].

Two systematic reviews completed by Lawn et al and Di Mari et al, have revealed several risk factors for third trimester stillbirth, such as: adolescent or elderly pregnancy; grand multi-parity; poor maternal nutrition, such as low body mass index or severe anemia; maternal medical conditions during pregnancy; exposure to toxic substances, such as tobacco, use of biomass for cooking or environmental toxins; and socio-economic deprivation, such as reduced access to healthcare services during pregnancy, either due to financial barriers or inadequate access to information [25, 26].

Among the few studies conducted in low and middle-income countries, a population-based cohort study in rural Ghana (a lower-middle-income country) found an association between antepartum stillbirth and previous stillbirth, increased maternal age (>35 years), primiparity, multiple pregnancies and no antenatal care attendance [27].

There have been, however, few studies conducted in low-income countries to identify preventable risk factors for intrapartum stillbirth, especially in settings where access to obstetric care is available [28]. Population-based studies conducted in low- and middle-income countries have shown that obstetric complications during the intrapartum period, such as preeclampsia, fetal mal-presentation, prolonged labor, preterm delivery, or cesarean section, are associated with intrapartum stillbirth [29-31]. A population-based study completed in Ghana revealed that poverty constituted the highest risk for intrapartum stillbirth and that this risk was not influenced by health care utilization [27]. A systematic review by Lawn et al examining risk factors for intrapartum stillbirth indicated that intrapartum stillbirth is preventable, as 25-67% of them are primarily due to preventable intrapartum complications such as prolonged labor [32]. There has been a paucity of information collected on the risk factors for antepartum and intrapartum stillbirth in low-income and middle-income countries where the majority of the stillbirths occur.

Preterm birth and small-for-gestational-age babies and their risk of neonatal death

In 2012, an estimated 15 million babies (11.3% of live births) worldwide were born preterm (born before 37 weeks of gestation), and about 13 million of those infants survived beyond the first month of life [17, 33-35]. A large proportion of these preterm births (37.6%) occurred in South Asia and accounts for a prevalence rate of 13.3% among all live births in the region [36].

An infant is considered small-for-gestational-age (SGA) when born with a birth weight below the tenth percentile according to a particular gestational age and sex-specific reference [7]. SGA can occur among infants who grew healthily in utero, but are naturally small. Alternatively, SGA can occur among infants who suffer from intrauterine growth restriction, which can be caused by a number of factors, including placental insufficiency, environmental exposures, and nutritional factors, for example [37]. In 2010, 32.4 million SGA infants were born worldwide, of which 2.8 million were also preterm [33]. Approximately 706,200 deaths were attributable to SGA, globally. More than half of SGA births occurred in South Asia, where the prevalence of SGA was 44.5% and the prevalence of preterm and SGA births was 2.9% in 2010 [36].

A meta-analysis on the association between neonatal mortality and preterm birth in East Africa showed that babies born at <34 weeks' gestation had a 58-fold increased risk of neonatal death than babies who were born at term [38]. Further, babies who were born between 34 and 36 weeks of gestation had a 3.2 times higher risk of neonatal death than babies who were born at term [38]. A pooled analysis conducted using data from low- and middle-income countries to determine the risk of neonatal mortality among preterm and SGA infants showed that babies who were preterm had a 6.8 times higher risk of death than babies born at term; SGA babies had a 1.83 times increased risk of neonatal death compared to AGA; and babies who were both had a 15-fold increased risk of neonatal mortality [39].

Premature babies or SGA have an increased risk of hypothermia, infection, respiratory distress syndrome (RDS), intracranial hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, neurodevelopmental impairment and mortality [37, 40, 41]. These complications could potentially be prevented, or minimized, with low cost interventions such as neonatal resuscitation, Kangaroo Mother Care and extra support for feeding, case management of babies with signs of infection, safe oxygen management and supportive care for RDS, hospital care of babies with RDS, use of continuous positive airway pressure (CPAP), and surfactant, or intensive neonatal care [42-45].

Neonatal resuscitation for reducing perinatal mortality

Initiation of breathing is critical in the physiologic transition from intra-uterine to extra-uterine life [46]. The time between a hypoxic event during labor or delivery and death can be very short—a baby who does not breathe at birth could die in less than an hour [17]. Between 5–10% of all newborns require assistance to establish breathing at birth and simple warming, drying, stimulation and resuscitation may reduce neonatal mortality and morbidity [47-52]. Neonatal resuscitation is defined as the set of interventions at the time of birth to support the establishment of breathing and circulation [52]. Of the 136 million births annually, an estimated 10 million of non-breathing babies require some level of intervention during the first minute after they are born—the "Golden minute™"[53]. Some non-breathing babies with primary apnea will respond to simple stimulation alone, such as drying and rubbing. Basic resuscitation with bag and mask is required for 3–6% of the babies and is sufficient to resuscitate most neonates with secondary apnea as their bradycardia primarily results from hypoxemia and respiratory failure [52]. More advanced measures, including endotracheal intubation, chest compressions and medication, are required in <1% of births and most of these require intensive care [54].

Observational studies conducted to evaluate the effect of neonatal resuscitation on birth outcomes have reported that these interventions reduce stillbirth and neonatal mortality [49, 55-58]. Observation is the preferred method in this area because it would be unethical to conduct a randomized controlled trial on the effectiveness of neonatal resuscitation on individuals (treatment versus placebo) [59]. A cluster randomized controlled trial in county hospitals in China to study the effect of a neonatal resuscitation program reported improvement in the knowledge, skills and confidence of health workers, as well as a reduction in the incidence of birth asphyxia and asphyxia-related deaths [60]. A cluster randomized controlled trial on the effect of a one-day standard newborn resuscitation training course on health worker practices in Kenya has reported a significant improvement in health workers' practices immediately after the training [61]. A systematic review on standardised formal neonatal resuscitation training (SFNRT) programs has shown that there is an improvement in acquisition of knowledge and skills as well as retention of knowledge in health workers, in addition to improvement in resuscitation and behavioral scores after the training has been provided. Three community-based cluster randomized trials in developing countries comparing SFNRT with basic resuscitation training (Early Newborn Care) reported decrease in early neonatal mortality. The SFNRT with team training has shown to increase any teamwork behavior and decreased resuscitation duration [62]. A meta-analysis of facilities-based studies, showed that the effect of facility-based basic neonatal resuscitation (in addition to stimu-

lation) was a 30% reduction in intrapartum-related neonatal death (RR=0.70, 95% CI 0.59–0.84) [46]. In that review, a study employing the expert Delphi method suggested that immediate newborn assessment and stimulation resulted in a 10% reduction in intrapartum-related deaths and a 10% reduction in preterm deaths [46].

Challenges for neonatal resuscitation

Despite the evidence that neonatal resuscitation has an effect on improving neonatal survival and reducing stillbirth burden, challenges remain in terms of ensuring the implementation of the standard neonatal resuscitation protocol into routine practices [47, 63-65]. There are several barriers to standard neonatal resuscitation and pediatric care in health facility settings, such as lack of standard training procedures, unavailability of resuscitation equipment at the time of birth, lack of periodic skill practice and assessment, lack of motivation, and a lack of hospital and clinical leadership to improve clinical performance [66-70].

Although SFNRT is known to improve the knowledge and skills of health workers immediately after the training, skill retention depends on the frequency with which the skill is performed and retraining is conducted [71-73]. However, there are significant cost implications in sending all health workers on resuscitation courses, and the re-certification time periods for the courses are often too infrequent for optimal skill retention. To re-certify more frequently would be impractical in terms of absence from work, availability of instructors required to teach, and other necessary resources [71].

There are a number of educational strategies that have been shown to improve the competencies and performance of health workers for a number of other clinical guidelines [74-81]. However, strategies to translate these clinical competencies into clinical practice for neonatal resuscitation have not yet been evaluated.

Helping Babies Breathe to improve quality of care at birth

With the understanding that there are limited resources and time available to the health workers to obtain training on neonatal resuscitation in low-income settings, the American Academy of Pediatrics developed a simplified neonatal resuscitation protocol and training package; Helping Babies Breathe® (HBB) [82]. The training package consists of a pedagogic method to train the birth attendant on essential neonatal resuscitation [83]. It is based on evidence from a neonatal evaluation study conducted by ILCOR (International Liaison Committee on Resuscitation), and recognizes that in many

countries only one birth attendant is present to provide care to both the mother and the newborn [84, 85].

The educational material of HBB consists of a well-tested pictorial representation of the resuscitation protocol, a learner workbook, facilitator flip chart, neonatal simulator and the required equipment, that is to say, reusable ventilation bag-and-mask devices and bulb suction devices [83, 86]. An evaluation of the HBB program in Tanzania showed that intrapartum-related stillbirth and early neonatal mortality was reduced by 24% and 47% respectively and that HBB is a low-cost intervention [87, 88]. HBB training evaluation in Ethopia showed that the neonatal resuscitation knowledge of health workers improved immediately after training [89]. In terms of the retention of competency in neonatal resuscitation skills after HBB training in Rwanda, the competency of neonatal resuscitation dropped to an unsatisfactory level, three months after the training, indicating that training alone was not adequate enough to retain the health workers' competency [90]. Several studies completed in high-income and low-income countries have shown that resuscitation competence improves immediately after the training, however, the resuscitation skill tends to deteriorate over a period of time [90-96]. With the provision of retraining on HBB in a rural hospital in Tanzania, the proportion of providers who were competent in simulated routine care and neonatal resuscitation scenarios increased after HBB training and this simulated setting competency remained at seven months after the training; however, the improvement did not transfer into clinical performance [97]. These studies suggest that HBB training and re-training is required to improve and maintain the competency in neonatal resuscitation, however, translating the clinical competency into routine performance requires a multi-faceted educational strategy. Thus, there is a need to further evaluate different implementation strategies to promote retention of resuscitation skills as well as to translate these into clinical practice so that lives can be saved.

Nepal—setting up the context

With a human development index of 0.54, reported in 2014, Nepal ranks 145 out of 187 countries [98]. As of 2011, 25.2% of people are living below the poverty line in Nepal; this represents a 5.7% decline in absolute poverty from 2004 when 30.8% people were living under the poverty line [99]. Among the employed population, 60% are engaged in the agriculture sector; however, the contribution of the agriculture sector to the GDP has declined from 61% in 1981 to 31% in 2011, while the contribution of the service sector has increased from 27% to 48% during this period [99]. In 2011, 67% of Nepalese were literate with female literacy increasing from 43% in 2001 to

58%. Similarly, 69% of the population attended school. The current life expectancy of Nepalese at birth is 66.6 years. The life expectancy of females has overtaken males in the last 30 years. Life expectancy at birth for females has increased from 48.1 years in 1981 to 67.9 years in 2011 [99].

Nepal has a population of 26.5 million with an estimated 724,000 births every year. As compared to the last three decades, the population growth rate has hovered around 2–2.5%, the growth rate has declined to 1.35%. The decline in population growth has been attributed both to a decline in fertility and emigration of youth [99].

Nepal has made steady progress on improving the overall health outcomes of its citizens. In particular, the country has made impressive progress on child survival and maternal health, which are targets 4 and 5 of the MDGs respectively. The target set for MDG 4 was to reduce the under-five mortality rate by two-thirds between 1990 and 2015 with an average annual decline of 4.4% [9]. Between the period of 1990 and 2014, there has been an unprecedented decline in under-five mortality in Nepal: it has decreased by 73% from 142 per thousand live births in 1990 to 38 in 2014 [100-103]. During this period, infant mortality has also decreased by 67%: from 99 per thousand live births to 33 [100-103]. According to the estimates of the United Nations (UN) agencies, maternal mortality in Nepal has declined by 76% from 790 per 100,000 live births in 1996 to 190 in 2013.

However, neonatal mortality has not decreased proportionately, with only a 57% reduction during the same period, that is to say, 53 per thousand live births in 1990 to 23 in 2014[100-103]. As of 2014, neonate deaths (i.e. deaths during the first 28 days of life) constitute 61% of under-five mortality in Nepal. Thirty-six percent of neonatal deaths take place on the day of birth, and 73% of neonatal deaths within the first week of life. Intrapartum-related condition, preterm-related complications, and infection, account for 27%, 29% and 28% of neonatal deaths in Nepal, respectively [17]. In 2014, 14% of babies were born preterm and 39.3% were SGA at birth in Nepal [36].

Nepal reported an estimated stillbirth rate of 22.4 per thousand births in 2011, with 54% of these deaths occurring during the antepartum period [17, 103]. Since then, the reduction in the stillbirth rate has been slow.

Rationale for the study in Nepal

To mitigate the number of stillbirth and neonatal deaths in Nepal from preventable causes, the Government of Nepal developed a National Neonatal Health Strategy to provide guidance on the neonatal interventions required

within each tier of health services in 2004 [104]. In 2006, the Government of Nepal developed the National Safe Motherhood and Neonatal Long Term Plan 2006 to integrate these neonatal interventions within the maternal health services [105]. Realizing that the time of birth is the highest period of risk for both mother and neonates, a skilled birth attendant training package was developed in 2007 [106, 107]. Since then, investments were made to train the doctors, nurses and axillary nurse midwives with the skilled birth attendant package to prepare them to competently manage any complications they might encounter when caring for mothers and babies at prenatal, birth and during the postpartum periods.

To increase access to and meet the demand for maternal and neonatal care, the Government of Nepal has provided free antenatal care, delivery and postnatal care since 2005 [108]. Since then, there have been improvements in the access to antenatal and delivery care by skilled providers with two-thirds of women accessing antenatal care from a skilled provider and half of the women delivering in the care of a skilled birth attendant [103]. Despite these investments, providing quality of care during the antenatal and intrapartum period remains a challenge for the country. Of the women who attend regular antenatal checkups, only 61% of women receive adequate antenatal care (e.g. blood pressure examination, urine and blood tests) [103]. The performance of the health workers responsible for neonatal resuscitation and intrapartum care is poor [89, 109].

Improvement in the quality of intrapartum care to reach the global MDG target will be crucial as more than one third of babies in Nepal die on the day of birth and a similar proportion die due to intrapartum-related conditions. In the clinical setting there are several factors that contribute to the poor performance of health workers, such as lack of knowledge, skills, motivation, and an enabling working environment. Understanding the barriers to improved performance at the time of birth will help to develop an intervention for improvement. Furthermore, to improve the survival rate of babies, both in utero and neonates, obtaining an understanding of the risk factors for death will be critical, and this understanding will also help to develop interventions to prevent and manage these risk factors.

The Government of Nepal is committed to improving neonatal survival as a signatory to the global plan, ENAP. The ENAP has set a target to reduce the stillbirth rate to l0 or less per thousand births and the neonatal mortality rate to 10 or less per thousand live births by 2035.

Conceptual framework

The conceptual model adopted in this thesis is based on the guideline developed by the Child Health and Nutrition Research Initiative (CHNRI) to set priorities for health research in a systematic way [110-112], as follows:

i. Health research to assess the burden of a health problem (disease and its determinant): descriptive research to understand the risk factors, measuring the prevalence. *For this priority, the thesis aimed to describe the risk factors of antepartum and intrapartum stillbirth and neonatal death.*

ii. Health research to improve performance of existing capacities to reduce the burden: discover the underlying problem within the health system and identify interventions to improve the performance. *The thesis explored the baseline adherence of the health workers for neonatal resuscitation.*

iii. Health research to develop new capacities to reduce the burden: development of new interventions or adapting or improving existing interventions. *The thesis aimed to adapt the Helping Babies Breathe protocol into the hospital context and develop continuous quality assessment and improvement cycle to improve the clinical competency, performance and perinatal outcomes.*

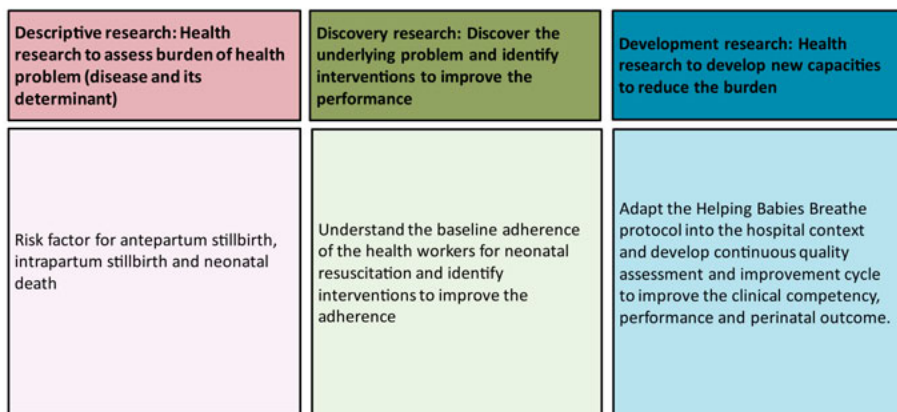| Descriptive research: Health research to assess burden of health problem (disease and its determinant)	Discovery research: Discover the underlying problem and identify interventions to improve the performance	Development research: Health research to develop new capacities to reduce the burden
Risk factor for antepartum stillbirth, intrapartum stillbirth and neonatal death	Understand the baseline adherence of the health workers for neonatal resuscitation and identify interventions to improve the adherence	Adapt the Helping Babies Breathe protocol into the hospital context and develop continuous quality assessment and improvement cycle to improve the clinical competency, performance and perinatal outcome.

Figure 4. Conceptual Framework for improving adherence to neonatal resuscitation to reduce perinatal death

Objectives

The main objective of this thesis is to evaluate the impact of the Helping Babies Breathe (HBB) quality improvement cycle on clinical competency, performance and perinatal outcome in a tertiary hospital in Nepal.
Specific objectives:

1. To identify the risk factors associated with antepartum stillbirth (paper I).

2. To identify the risk factors associated with intrapartum stillbirth (paper II).

3. To assess the level of risk for neonatal mortality among babies who were born prematurely and/or SGA (paper III).

4. To assess the health workers' adherence to neonatal resuscitation before implementation of Helping Babies Breathe (paper IV).

5. To evaluate the different implementation strategies (Quality Improvement Cycle) for HBB on change and retention of the knowledge and skills on neonatal resuscitation (paper V).

6. To evaluate the adherence to the neonatal resuscitation protocol and reduction in perinatal mortality after implementation of HBB QIC (paper VI).

In the following chapter, I will explain the methodology, results, discussion and conclusion for all of these papers.

Methods

Study setting

The study for this thesis was conducted in a tertiary hospital in Kathmandu; the Nepal-Paropakar Maternity and Women's Hospital. The hospital is a publicly funded hospital, which provides obstetric and gynecological services and is the referral center. The hospital has 425 beds with a 240 health workforce. The hospital provides antenatal, delivery and postpartum services for women and has a level II neonatal care unit. The hospital has an annual delivery rate of approximately 22,000 with a stillbirth rate of 19 per thousand deliveries, and an early neonatal mortality rate of 9 per thousand live births [113].

There are three delivery units in the hospital: a maternal and newborn service center (MNSC), a labor unit and an operation theatre. The low-risk vaginal deliveries take place in the MNSC, which is staffed with nurse-midwives; high-risk vaginal deliveries take place in the labor unit, which is staffed with nurse-midwives and medical doctors; and in the operation theatre, which is staffed with anesthesiologists, obstetricians, medical doctors and nurse-midwives, high-risk vaginal deliveries and cesarean sections take place (Table 1).

In each delivery room there is a neonatal resuscitation corner where the resuscitation of newborns takes place.

The hospital also has a Kangaroo Mother Care Unit for the management of preterm or low birth weight babies. The annual admission rate in the unit is approximately equal to 900.

Babies who have complications at birth or during the postpartum period are treated in the special newborn care unit, which is staffed with pediatricians, doctors and nurses. The special newborn care unit provides treatment for perinatal depression, hyperbilirubinemia, neonatal sepsis and respiratory distress syndrome. The annual admission rate in the special newborn care unit is approximately equal to 2,400.

Table 1. Human resources and set-up of each delivery unit

Delivery units	Type of Health workers (HW)	Number of HW	Number of delivery beds	Type of delivery service	Number of neonatal resuscitation tables
Maternal and Newborn Service Center room	Nurse-midwives	11	8	Low-risk delivery	1
Labor room	Obstetricians, medical doctors, nurse-midwives, medical and nurse students	11	9	Low- and high-risk delivery	3
Operation room	Anesthesio-logist, obs-tetricians, medical doctors, nurse-midwives	11	1	Cesarean section	1

Study design and methods

This thesis is based on the study trial to evaluate the impact of simplified neonatal resuscitation protocol-Quality Improvement Cycle to improve the health workers' neonatal resuscitation clinical competency and performance, and perinatal outcomes.

The first two papers of this thesis provides the risk factors for antepartum and intrapartum stillbirth, the third paper describes the level of mortality risk in preterm or/and small for gestational age babies, the fourth paper describes the health workers' adherence to neonatal resuscitation guidelines before the implementation of the HBB QIC, the fifth paper reports on the evaluation of HBB QIC on the retention of neonatal resuscitation knowledge and skills six months after the completion of training, and the final paper reports on the impact of the HBB QIC on health workers' performance and perinatal outcomes.

Table 2. Study design and methods for the papers included in this thesis

Paper	I	II	III	IV	V	VI
Research question	What are the risk factors for antepartum stillbirth?	What are the risk factors for intrapartum stillbirth?	What is the level of mortality risk for babies who are born prematurely or/and small-for-gestational age?	What is the baseline adherence to neonatal resuscitation protocol before the implementation of HBB?	Which component of HBB QIC determines the retention of neonatal resuscitation skills?	What is the impact of HBB QIC on health workers' performance and perinatal outcomes?
Study setting	Tertiary hospital of Nepal					
Period	July, 2012–September, 2013	July, 2012–September, 2013		July–October, 2012	December, 2012–July, 2013	July, 2012–September, 2013
Design	Case-control	Case-control	Case-control	Cross-sectional	Time-series	Cohort with nested case-control design
Data collection method	Clinical record review, interviews with the mothers	Clinical record review, interview with the mothers	Clinical record review, interview with the mothers	Video observation of the clinical case management of babies who were resuscitated and clinical record review	Knowledge and skill assessment, direct observation of the health workers' participation in the QI process	Clinical record review, interview with mothers, video observation of the clinical case management of babies who were resuscitated
Sample	307 case population (antepartum stillbirth) and 4,505 control population (intrapartum stillbirth and live birth)	136 case population (intrapartum stillbirth) and 4,476 control population (live birth)	299 case population (death within 28 days of birth) and 4,413 control population (babies who were alive at 28 days of birth)	1,827 newborns who are resuscitated	137 health workers	25,108 deliveries with 299 neonatal deaths, 136 intrapartum stillbirth and 307-antepartum stillbirth. 1,076 control newborns who were resuscitated.
Outcome	Antepartum stillbirth	Intrapartum stillbirth	Preterm or small-for-gestational age related neonatal mortality	Adherence to neonatal resuscitation protocol	Neonatal resuscitation skills before HBB QIC, immediately after training and 6 months after training	Perinatal mortality rate, antepartum mortality rate, Intrapartum stillbirth rate, first day neonatal mortality rate

Case-control design for risk factor analysis papers I, II and III

For the risk factor analysis papers, unmatched case-control design was used. The control population was 20% of the randomly-selected women at the time of admission for delivery in the hospital. A lottery technique was used to select the control population. The study period was from July 2012 until September 2013.

For the first paper, all women with antepartum stillbirth occurring during the study period were included as cases. Any antepartum stillbirth that occurred in the control population were excluded and re-categorized as case population.

For the second paper, all intrapartum stillbirths that occurred after hospital admission, that is to say, woman who were in labor and had fetal heart sound at admission, were included as cases. Women who had fetal death at admission, that is to say, absence of fetal heart sound, were excluded from the case population. Any women with antepartum stillbirth occurring in the control population were excluded and any women with intrapartum stillbirth occurring in the control population were excluded and re-categorized as case population. The control population for this paper included all women with live births who had either a vaginal birth or indicated cesarean delivery.

For the third paper, all the women with neonatal death occurring during the study period were included as cases. Any antepartum or intrapartum stillbirth occurring in the control populations were excluded. To assess the outcome of the category of live birth until 28 days of life after discharge, a follow-up phone interview was conducted to all control women with live birth at the 29th day of birth. Any neonatal deaths occurring in the control population were excluded and re-categorized as case population for this paper.

Cross-sectional study for Paper IV: Baseline adherence of the health workers to neonatal resuscitation protocol

For this paper a cross-sectional study was conducted, and all of the babies who were resuscitated from July 1 to October 31, 2012 were included in this study.

Paper V: Evaluation of HBB QIC on retention of neonatal resuscitation skills 6 months after training

For this paper, a time series design was used and the research was conducted from January to September, 2013. The nurses and doctors in the admission unit, antenatal ward, labor unit, MNSC, operation theatre and postnatal ward

were enrolled as the participants. There were a total of 137 participants for this study. The knowledge and skills of the participants were assessed using the standard tools of the HBB package. Assessment using the tool was conducted before the implementation of HBB QIC, immediately following the HBB training, and 6 months after the training. Information on health workers' implementation of quality improvement cycle-daily skills check, preparation at birth, self-evaluation checklist use, completion of peer evaluation, and attendance at the weekly review and reflection meetings was assessed using a direct observation checklist.

Paper VI-Evaluation of HBB QIC on adherence to HBB protocol and change in perinatal mortality

For this paper in the thesis, a prospective cohort study was conducted to evaluate the change in the mortality and stillbirth rates before and after implementation of HBB QIC. All the stillbirths and neonatal mortality occurring during the study period were included for this study and the neonatal mortality rate and stillbirth rate were calculated. A nested case control was completed to evaluate the change in the risk of mortality outcomes (perinatal mortality, stillbirth, intrapartum stillbirth, first day neonatal mortality) before and after implementation of HBB QIC. The reference population for the nested case control was 20% of the randomly-selected women at the time of admission. Among the control population selected, that is to say, those babies who were brought to the resuscitation table for resuscitation, video recordings of the resuscitation table activities were observed to access the change in the performance of the health workers before and after the implementation of HBB QIC. For this paper the study period was from July 1, 2012 to September 30, 2013.

Intervention

Planning of the Quality Improvement Cycle

In November 2012, the study team organized a half-day review workshop with hospital leadership, including the hospital director, administrator, head of the pediatric department, nursing matron, nursing supervisors and unit incharges. During this workshop, the current practices on neonatal resuscitation and intrapartum outcomes were discussed based on an interim analysis of the data from the elapsed four-month baseline period. A root-cause analysis of neonatal resuscitation practice was conducted, which identified the inadequate adherence to current practice recommendations and possible causes for this [114-116]. The study team familiarized the workshop participants with the concept of a QIC. A multi-disciplinary quality improvement

team (QIT) of the workshop participants was formed with the hospital direc-tor as the leader. The QIT decided to reconvene to develop a QIC with the aim of improving adherence to neonatal resuscitation protocols at the hospi-tal.

The QIT conducted meetings with the staffs at each delivery unit to discuss the causes of inadequate adherence to clinical practice and how to improve it. These meetings identified the need for continuous skill enhancement, equipment support, and periodic review and reflection meetings. As a result of the meetings, the hospital decided to set a goal to reduce intrapartum-related death by 50% through HBB protocol training and subsequent im-provement of knowledge and adherence (Figure 5). The meeting identified five key quality improvement processes to improve the adherence to neona-tal resuscitation protocol:

1. Training on the HBB protocol
2. Being prepared for all births, that is, readiness for neonatal resuscitation for each birth
3. Bag-and-mask skill check on a mannequin on a daily basis
4. Self-evaluation on the managing of babies
5. Peer evaluation after neonatal resuscitation

To assess the progress of the implementation of the quality improvement process, the QIT planned to provide HBB training, conduct 12 sessions of weekly review and reflection meetings and refresher trainings as a part of the QIC. To monitor the progress of HBB QIC implementation, a progress board was created for placement at each delivery unit (Figure 6).

Continuous Quality Improvement Cycle to reduce stillbirth and neonatal death in our unit

What are we trying to accomplish? (aim)	To reduce the intrapartum related stillbirth and intrapartum related neonatal death by 50%
What changes can we make that will result in an improvement? (objective)	To improve the immediate care of non breathing baby instituting Helping Babies Breathe

How will we know if a change is an improvement? (measurement of change)	Change in the intrapartum related stillbirth Change in the intrapartum related neonatal death Successful ventilation of non-breathing newborn Ventilation with 60 seconds of birth in non-breathing newborn

Act   Plan

Study   Do

"We run small cycles of change"
Paropakar Maternity and Women's Hospital Quality Improvement Team

Figure 5. Quality Improvement Cycle in the delivery units [116-118]

Operation Theatre	Week 1	Week2	Week3	Week 4
Macerated still birth				
Fresh Still birth				
Neonatal Death				
Non-breathing baby				
Non-breathing with B & M				
Non-breathing with B & M within 1 minute				
Resuscitation corner available				
Adequate and functional suction				
Adequate and functional Bag and Mask				
Mannequin for skill check				
Weekly Review meeting				1

Figure 6. Progress board in each delivery unit

Implementation of HBB QIC

During the first week of January 2013, a two-day training package on the HBB QIC was provided to all hospital staff working in the three delivery units. Immediately following the training week, bag-and-mask kits and Penguin Suction Devices^{TM} were provided to each delivery unit. Additionally, HBB mannequin was placed at the entry of each delivery unit for daily bag-and-mask skill checks; self-evaluation checklists were attached to each clinical record form; and HBB schematic posters were placed in front of each resuscitation table for peer review. Weekly review and reflection meetings were conducted to discuss progress on the implementation of HBB QIC standards.

Table 3. Description of the implementation strategies for Helping Babies Breathe (HBB) Quality Improvement Cycle (QIC)

Component	Activity	Facilitators and participants
HBB training	Two-day training. First day on HBB knowledge and skills as per standard package and second day on components of HBB QIC standards, training of trainers on how to conduct weekly review and reflection meeting, how to fill self-evaluation checklists and conduct peer evaluations.	Facilitators: HBB trainers Participants: Staff of the delivery units
Setting up HBB QIC standards	At each unit, development of QIC goals and objectives, development of a place for daily bag-and-mask skill checks, QIC weekly review and reflection meetings, use of self-evaluation checklists and peer reviews after each resuscitation.	Facilitators: Study team Participants: Staff of the delivery units
QIC Weekly review and reflection meeting	At each unit, the unit in-charge facilitates the weekly review and reflection meetings on the progress of implementation of HBB QIC standards.	Facilitators: HBB trainers Participants: Staff of the delivery units
Daily bag-and-mask skill check	At each unit, each staff member completes a bag-and-mask skill check on the mannequin before starting duty.	Facilitators: Unit in-charge Participants: Staff of the delivery units
Self-evaluation checklist after each delivery	A self-evaluation checklist, which consists of a list of steps for immediate newborn care and neonatal resuscitation as per HBB protocol with checkboxes. After completing care of each newborn, the nurse midwife will complete the self-evaluation checklist based on the steps taken as per the HBB protocol.	Facilitators: Unit in-charge Participants: Staff of the delivery units
Peer review after each resuscitation	A mounted poster with the steps of the HBB protocol will be displayed at each resuscitation table, so that peers can review with the colleague completing resuscitation on whether the steps were followed.	Facilitators: Unit in-charge Participants: Staff of the delivery units
Refresher training	A one-day training course provided to all the delivery unit staff on the HBB protocol.	Facilitators: HBB trainers Participants: Staff of the delivery units

Sample size

A power analysis based on the pre-study perinatal mortality and delivery rate at the hospital indicated that a reduction of 20% in perinatal mortality would be detectable within the set time frame (alpha 0.05, beta 0.20).

Data collection

A surveillance system was set up to collect socio-demographic, obstetric and postpartum information from the women in the case and control populations at the admission, delivery and postnatal units. A surveillance team member at the admission unit collected information from the women who were admitted to the hospital for delivery. The team randomly selected 20% of women admitted to the hospital using a lottery technique. The surveillance team members at the delivery and postnatal units followed the control women until discharge and followed up on the birth outcome through telephone interviews conducted 28 days after delivery. The surveillance team at the delivery and postnatal units also collected information on the case population, that is, all stillbirth and neonatal deaths that occurred in the hospital. Information about the case and control populations was taken from the women's individual clinical journals, including demographic characteristics, obstetric history, intrapartum clinical progress and outcomes, and neonatal information. For certain socio-economic information, short interviews were completed with the women from both the case and control populations.

CCD Cameras were used to collect data on the hospital's neonatal resuscitation routines. A total of 6 cameras were placed to cover each resuscitation table; one in the operating theatre, one in the maternal and newborn service center (MNSC), and four in the labor rooms (labeled 1–4). The cameras had a progressive scan sensor and excellent low light performance. The cameras were equipped with motion sensors that recorded all movement within the camera's field of vision. All film material recorded was sent to and stored on the main computer for data collection. Material captured by the CCD cameras that did not contain a resuscitation situation, such as equipment checks, infants other than newborn babies placed on the resuscitation table for observation, and staff using the table as support for updating medical records, were reviewed and disregarded as invalid.

The resuscitation cases recorded by the CCD cameras were matched to a Case Record Form, which contained the mother's name, identification number and admission number. This information was transferred to a CCD Observation Record Form, where a total of 12 sections had to be filled out using information obtained from the Case Record Forms. In addition to the

mother's name, ID number and admission number, these included date, time and place of birth, the baby's gestational age, Apgar-score at 1 and 5 minutes, birth weight, sex, and whether the baby was referred or not after the resuscitation.

The CCD Observation Record Form was then used to register information from the corresponding resuscitation case recorded by the CCD cameras. Surveillance officers, not in any way connected to the hospital or the staff, were trained in how to use the data collection software and how to fill in the Observation Forms. The form had 14 sections to be filled out regarding observations made when watching the camera recordings. These sections included place, date, and time of resuscitation, whether the baby was crying when resuscitation was initiated, which specific resuscitation techniques were used (i.e. stimulation, suction, oxygen and ventilation) and the time intervals at which they were performed, time of first cry, and outcome. The surveillance officers then had to sign the Observation Forms and hand them to the staff in charge of data management.

The knowledge and skills of nurse midwives and doctors were assessed using the standard tool of the HBB package, which has been validated and used in other settings where HBB knowledge and skill evaluation have been conducted. A questionnaire with 17 multiple choice questions was used to assess the knowledge of health workers on the HBB protocol, a 7-step checklist for bag-and-mask skill checks, a 5-step checklist for preparation at birth skill checks, a 13-step checklist with simulation for the first Objective Structured Clinical Examination (OSCE A), and an 18-step checklist with simulation for OSCE B.

Table 4. Evaluation of HBB QIC

	Thematic Area	Tools
Knowledge and skill competency	Knowledge assessment	17 multiple choice questions
	Bag-and-mask skill	7-step skill observation checklist
	Preparation at birth	5-step skill observation checklist
	OSCE A	13-step observation checklist
	OSCE B	18-step observation checklist
Clinical practice	Daily skill check	7-step skill observation checklist
	Preparation at birth	5-step skill observation checklist
	Self-evaluation checklist	21-step checklist
	Peer evaluation process	HBB schematic protocol
	Weekly review meetings	Notes of the meeting

Training on data collection

The surveillance team consisted of 12 public health professionals having 3 years of education in public health and had at least 1 year of experience in data collection and data management. An experienced research coordinator who had 5 years of experience in clinical studies and research led the team. A full-time data entry officer and a data manager were also employed on the study. The forms were developed in consultation with the obstetricians and pediatricians of the hospital and were field tested before using them for the study. A three-day training program was provided to the surveillance team on the correct completion of the forms. Piloting of the forms with the surveillance officers took place for a month in June 2012. After the piloting stage, the forms were printed and the research coordinator conducted continuous monitoring of the surveillance officers.

Data management

The surveillance officers completed and assessed the observational forms and the interview forms, followed by their thorough re-evaluation by a research coordinator. The data entry officer re-checked them for discrepancies before entering the data into a database. The research coordinator verified at least 10% of the observational forms for accuracy, ensuring that the information from their primary source was identical, as well as the observations made in the interviews. In order to avoid data loss, a protocol for a data tracking system was established. Similarly, bi-monthly internal and external verifications or audits were conducted to ensure data completeness and accuracy.

The Census and Survey Processing System (CSPro), a public domain software package developed and supported by the U.S. Census Bureau and ICF Macro, was used for quality data management. CSPro was interfaced with SPSS (originally, Statistical Package for the Social Sciences), which was used for statistical analysis, data management (case selection, file reshaping, creating derived data), and data documentation. Hard copies of records were stored in a filing system in a secure room. Data were checked for accuracy, consistency, and completeness in both the CSPro and SPSS software packages.

Data analysis

Risk factor for Antepartum Stillbirth (paper I)

For data analysis purpose, categorical variables were created from raw or continuous variables within the dataset.

Comparison of the demographic, social and obstetric characteristics among case and control populations was made using Pearson's chi-square and Fisher's exact test. A comparison of the mean and median maternal age in the two populations was made using a *t*-test.

For those demographic, social and obstetric characteristics that differed ($p<0.01$) between the two population groups, univariate logistic regression analysis was conducted to test the association between those variables and antepartum stillbirth.

For those variables which showed an association with antepartum stillbirth in the univariate logistic regression analysis, a multivariate model was created to determine whether the association between the potential risk factors and antepartum stillbirth remained after adjusting for confounders. The variables investigated were maternal age (continuous), maternal education, wealth index (poor or non-poor), antenatal care attendance, parity, previous stillbirth, antepartum hemorrhage, hypertensive disorder during pregnancy, and small-for-gestational age.

Risk factor for Intrapartum Stillbirth (paper II)

The comparison of demographic and obstetric characteristics of the women in the case and control populations was made using Pearson's chi-square test for categorical variables, as well as Fisher's exact test. Means and medians of maternal age were also compared. The variables were compared between the case and control populations: maternal age (categorical), maternal education, ethnicity, wealth quintile, ANC attendance, parity, previous stillbirth, antepartum hemorrhage, hypertensive disorder during pregnancy, medical disorder during pregnancy, multiple births, obstetric complications during labor, FHRM as per protocol, use of partogram, mode of delivery, sex of baby, weight for gestational age at birth, gestational age of baby, and a combination of weight for gestational age at birth and gestational age at birth.

Univariate logistic regression was conducted to determine the level of association between different demographic and obstetric characteristics and intrapartum stillbirth that showed a difference ($p<0.01$) between the case and control populations. Multivariate logistic regression analysis was conducted

to determine the level of association between the demographic and obstetric characteristics and intrapartum stillbirth for those that have shown association in the univariate model.

Level of mortality risk for babies born prematurely or/and small for gestational age (paper III)

The demographic, social and obstetric characteristics of the case and control populations were compared using a Pearson's chi-square test, Wilcoxon rank-sum, t-test or Fisher's exact test to assess whether there was a difference ($p<0.05$) between the two groups.

Univariate logistic regression analysis was completed to test the association between neonatal death and the demographic, social and obstetric characteristics of the women and babies that showed differences ($p<0.01$) between the case and control populations. Three different multivariable models were created to assess the level of association of neonatal mortality with preterm and/or SGA after adjusting for maternal age, maternal educational status, antenatal care attendance, wealth status, complication during the intrapartum period, mode of delivery, parity and multiple pregnancy. The first multivariable model assessed the level of association between neonatal mortality and preterm birth compared to term; the second multivariable model assessed the level of association between neonatal mortality and being born SGA compared to babies born AGA; and, the third model assessed the level of association between neonatal mortality and being born both preterm and SGA compared to being born only preterm, or only SGA, or neither.

Inadequate adherence to neonatal resuscitation protocol (paper IV)

The data collected from resuscitation cases were analyzed to assess the resuscitation routines at the hospital. These were then compared with existing guidelines. Relationships between the use of bag-and-mask ventilation and factors such as sex, birth weight, mode, and time of delivery and were also analyzed.

Fifty CCD camera recordings were randomized out of 257 recorded in October and November 2012. To evaluate the inter- and intra-rater reliability of the observational forms, two independent observers completed two sets of forms for each case, with roughly 6 weeks in between the two viewings conducted by each observer.
Out of the 14 original sections in the observational form, 12 were used when analyzing the reliability. Place and date of the resuscitation were filled out in

order to match the two sets of forms together, and thus were not included in the analysis. Using the time intervals given for each of the four individual resuscitation techniques, the total time each technique was performed was calculated and analyzed as four additional variables. The total time from when the baby was placed on the resuscitation table until the first cry was also calculated. In total there were 17 variables individually analyzed and cross-compared in each resuscitation case. A confidence level of 95% was considered significant.

Evaluation of HBB QIC on retention of neonatal resuscitation skills 6 months after training (Paper V)

The background characteristics of the health workers included in the analysis were age, professional experience, number of deliveries attended per month, number of neonatal resuscitations conducted per month and academic qualifications. The mean ± SD and median (IQR) for age of the health worker was calculated; mean and median years of professional experience in midwifery was calculated; and the mean and median number of deliveries and resuscitation attended per month was calculated. Academic qualifications were categorized into two groups; those who had completed intermediate level education in nursing or who were axillary nurse midwives versus those who had completed bachelor of nursing or above.

The mean numeric scores obtained on the knowledge questionnaire, preparation at birth checklist, bag-and-mask skill check, and OSCEs A and B at baseline, immediately after the training and 6 months after the training were compared using a paired t-test. The proportion of health workers who scored $\geq 80\%$ in bag-and-mask skill check before the training, immediately after the training and 6 month after the training was compared using paired t-test.

The retention of the bag-and-mask skill was calculated based on the change of bag-and-mask skill score immediately after the training and six month after the training. The health workers who scored the same or more at six months after training than immediately after training were categorized as having retained the skills.

Analysis of the association ($p<0.01$) between the health workers who retained the skills with their daily bag-and-mask skill check, preparation for every birth, use self-evaluation checklist, peer evaluation after each resuscitation and attendance of health worker in the weekly review meeting was completed using the Fischer's exact test.

Logistic regression analysis was conducted to assess the level of association between the education strategies of HBB QIC with retention of bag-and-mask skills at 6 months.

Evaluation of HBB QIC on adherence to HBB protocol and change in perinatal mortality (Paper VI)

Pearson's Chi-square test was used to compare mortality-related outcomes among the cohort population during the baseline and intervention periods. Background characteristics of the control population were compared between baseline and intervention groups using Wilcoxon rank-sum tests and Pearson's chi-square test. Statistical significance was decided at a p-value of below 0.05.

Multiple logistic regression analysis was used to determine if the implementation of the HBB QIC was associated with a change in outcome measures of cases, compared with the control population. To create the multiple logistic regression model, adjustments were made for the background characteristics that were significantly different between the baseline and intervention control populations. Univariate logistic regression analysis was conducted within the control population to identify any change in health workers' practice of neonatal resuscitation after implementation of HBB QIC.

To the greatest extent possible, missing data for primary and secondary outcomes were minimized; however, there were missing data for some background characteristics of mothers, therefore we used the multiple imputation method to deal with data missing at random [119].

Ethical considerations

The Nepal Health Research Council (Reg. No. 37/2012) and the Ethical Review Board of Uppsala University (dnr 2012/267) provided ethical approval for the study. Several interactive meetings were held with hospital administration and health workers to conceptualize the research. Discussions were also held with academicians, researchers, policy makers, and representatives of local and international non-governmental organizations and associations where the plans and objectives of the research were presented. A written consent form was developed for potential control participants to see whether or not they were willing to participate. The study worked with the respondents only after their consent was recorded. The surveillance officers conducted follow-up phone interviews with the mothers of babies in both the case and control samples until the 29th day of birth.

The study team formed a Data Monitoring Committee in June 2012 to be convened on a 6-monthly basis thereafter. The board included national and international experts for the trial and reviewed the data and procedures according to the standard guidelines. Apart from checking the adequacy of enrolment, the committee ensured that the study protocol was followed. It also reviewed interim data for completeness, quality, and adherence to ethical requirements, and, accordingly, made recommendations on the continuation of the trial or its modifications.

Results

A total of 443 stillbirths occurred during the study period; 307 were antepartum stillbirths and 136 were intrapartum stillbirths. A total of 299 neonatal death occurred, with 209 dying in the first seven days of life and 78 in first 24 hours of life. There were a total of 25,108 deliveries during the study period.

Risk factors for stillbirth and neonatal death

Risk factors for Antepartum stillbirth

In the study, women who had no antenatal care had a fourfold risk of antepartum stillbirth than those who had antenatal care (aOR 4.2, 95% CI 3.2–5.4). Women who had antepartum hemorrhage had a fourfold risk of antepartum stillbirth than those who did not have the complication (aOR 3.7, 95% CI 2.4–5.7). Women who had previous stillbirth had a threefold risk of antepartum stillbirth than those who did not have previous stillbirth (aOR 2.6, 95% CI 1.6–4.4) (paper I) (Table 5).

Risk factors for Intrapartum stillbirth

In the study, women who had obstetric complications during the intrapartum period had a fourfold risk for intrapartum stillbirth than women who had no obstetric complications (aOR 4.5, 95% CI 2.9–6.9). Women whose fetal heart rate monitoring was done at more than half-hour intervals had a twofold risk of intrapartum stillbirth than women whose fetal heart rate was monitored on a half-hour basis (aOR 1.9, CI 95% 1.5–2.4). Women who had premature birth had a fivefold risk of intrapartum stillbirth than women who had a term birth (aOR 5.4, CI 95% 3.5–8.2) (paper II) (Table 5).

Risk factors for neonatal death

In the study, the babies who were born preterm had 12 times the risk of neonatal death than those babies who were born at term (aOR 12.4, 95% CI 8.1–18.9). Babies who were born with small weight as per gestational age had a 40% higher risk of neonatal death than babies who were born at an appropri-

ate weight for gestational age (aOR 1.4, 95% CI 1.1–1.8). Babies who were both prematurely born and had a small weight for gestational age had a 16 times higher risk of neonatal death than those who were born at term and had an appropriate weight for gestational age (aOR 16.2, 95% CI 12.3–21.3) (paper III) (Table 5).

Table 5. Multi-variable analysis of risk factors for antepartum, intrapartum still-birth and neonatal mortality

	Antepartum stillbirth		Intrapartum still-birth		Neonatal Mortality	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Maternal age in years	1.0	0.9–1.1	1.0	0.9–1.1	1.0	0.9–1.0
Poverty	1.3	1.0–1.8	1.8	1.1–3.4	1.0	0.7–1.5
Primary education or less	2.4	1.7–3.2	3.2	1.8–5.5	1.8	1.3–2.5
Parity	1.2	1.0–1.3	1.2	1.0–1.5	1.3	1.1–1.6
No antenatal care	4.2	3.2–5.4	4.8	3.2–7.2	4.0	3.0–5.4
Multiple pregnancy	0.7	0.3–1.9	1.6	0.6–3.8	1.3	0.6–2.8
Antepartum hemorrhage	3.7	2.4–5.7	2.1	1.1–4.2	0.8	0.6–1.5
Hypertensive disorder during pregnancy	2.1	1.5–3.1	0.9	0.5–1.8	0.7	0.3–1.8
Obstetric risk factor during the intrapartum period	-	-	4.5	2.9–6.9	2.2	1.6–3.2
Fetal heart rate monitoring	-	-	1.9	1.5–2.4	0.8	0.7–1.3
Partogram	-	-	2.1	1.1–4.1	0.7	0.6–1.4
Indicated cesarean section	-	-	0.5	0.3–0.7	0.8	0.7–1.9
Small-for-gestational-age	1.5	1.2–2.0	1.8	1.2–1.7	1.4	1.1–1.8
Preterm birth	-	-	5.4	3.5–8.2	12.4	8.1–18.9
Preterm and small-for gestat-ional-age	-	-	9.0	7.3–15.5	16.2	12.3–21.3

Adherence to neonatal resuscitation before HBB QIC implementation

During the baseline study on the adherence to neonatal resuscitation, of the total babies who received resuscitation at birth, 46.7% of them were either crying or breathing at birth. Of these, 85% received suctioning, 23% of them received stimulation, 20.5% received oxygen support and 1.2% received bag-and-mask ventilation. For babies who were not crying/breathing, 92% of them were suctioned, 64.4% were stimulated, 52% of them were provided oxygen support and 16.6% received bag-and-mask ventilation (Paper IV) (Table 6).

Among the not crying/breathing babies, boys received 44% more ventilation (aOR 1.44, CI 95% 1.01–2.06) than girls, babies who weighed less than 2500 grams received 68% more ventilation (aOR 1.68, CI 95% 1.13–2.51) than babies weighing 2500 grams, and babies who were delivered by cesarean section received 64% more ventilation (aOR 1.64, CI 95% 1.14–2.36) than those who were born vaginally (Paper IV).

Table 6. Intervention for neonatal resuscitation at the resuscitation table

	All newborns brought to table		Newborns crying when brought to table		Newborns not crying when brought to table	
Action taken	*n*	*%*	*n*	*%*	*n*	*%*
Stimulation						
Yes	824	45.1	197	23.1	627	64.4
No	1,003	54.9	656	76.9	347	35.6
Bag and mask						
Yes	172	9.4	10	1.2	162	16.6
No	1,655	90.6	843	98.8	812	83.4
Suction performed						
Yes	1,624	88.9	725	85.0	899	92.3
No	203	11.1	128	15.0	75	7.7
Oxygen provided						
Yes	687	37.6	175	20.5	512	52.6
No	1,140	62.4	678	79.5	462	47.4

Competency on neonatal resuscitation before, immediately after training and six months after implementation of HBB-QIC

Immediately following the HBB training, the skills for neonatal resuscitation in health workers improved. There was a significant change ($p<0.001$) in the mean skill score after the HBB training; 2.3 ± 0.5 before compared to 6.7 ± 0.6, and the skill was retained 6 months after the training (6.7 ± 0.5) ($p=0.8$). There was a significant change ($p<0.001$) from baseline in the mean knowledge score, skills scores for preparation at birth, OSCE A, and OSCE B after the training and these were retained 6 months after the training. There were no health workers who were competent in bag-and-mask skill before the training, 93% of health workers were competent immediately after the training ($p<0.001$) and 99% of the health workers were competent six months after the training (Paper V).

More than half of the health workers practiced their bag-and-mask skills daily, 61% of them prepared for each birth, 82% of them did self-evaluation after every birth, 43% of them did peer evaluation after each resuscitation and 85% of them attended weekly review and reflection meetings. There was a positive association ($p<0.01$) between health workers who did bag-and-mask skill checks daily, prepared for resuscitation before every birth, used the self-evaluation checklist and attended weekly review meetings each month (Paper V) (Table 7).

Table 7. Association between the different implementation strategies of the Helping Babies Breathe (HBB) Quality Improvement Cycle (QIC) and the retention of bag-and-mask skills

		Non-retention (*N*=27)	Retention (*N*=110)	*p*-value
Daily bag-and-mask skill checks	Yes	6 (8.5%)	65(91.5%)	*p*=0.001
	No	21 (31.8 %)	45 (68.2%)	
Preparation at every birth	Yes	12(14.3%)	72(85.7%)	*p*=0.038
	No	15 (28.3%)	38 (71.7%)	
Use of self-evaluation checklist	Yes	17 (15.2%)	95(84.8%)	*p*=0.008
	No	10 (40.0%)	15 (60.0%)	
Peer evaluation after each resuscitation	Yes	12 (20.3%)	47 (79.7%)	*p*=0.5
	No	15 (19.2%)	63 (80.8%)	
Attendance of weekly review meetings	Yes	20 (17.1%)	97 (82.9%)	*p*=0.065
	No	7 (35.0%)	13 (65.0%)	

The regression analysis showed that health workers who conducted daily bag-and-mask skill checks had 5 times more chance of retaining the skill than those who did not conduct daily bag-and-mask skill checks (RR 5.1, 95% CI 1.9–13.5). Health workers preparing for resuscitation for every birth had a twofold chance of retaining the skills than those who did not prepare (RR 2.4, 95% CI 1.0–5.6). Health workers using self-evaluation checklists after each birth had a fourfold chance of retaining the skills than those who did not use them (RR 3.8, 95% CI 1.4–9.7). Health workers attending the weekly review meetings had 2.6 times more chance of retaining the skills than those who did not attend (RR 2.6, 95% CI 1.0–7.4) (Paper V).

Health Workers' performance on neonatal resuscitation and perinatal outcomes after implementation of HBB QIC

There was a sharp decline in the intrapartum stillbirth rate and first-day neonatal mortality in the first three months of intervention when the HBB QIC training was completed, after 12 cycles of QIC weekly review and reflection meetings were completed, and when the daily bag-and-mask skill checks, self-evaluation, peer review and progress board use and daily briefs to QIT were conducted. The change was sustained from the fourth to sixth months when daily bag-and-mask skill checks, self-evaluation, peer review and progress board use and daily briefs to QIT were continued. There was a slight decline in the intrapartum stillbirth rate, first-day neonatal mortality and a slight increase in the bag-and-mask ventilation within one minute when refresher HBB training was conducted at the seventh month and when the daily bag-and-mask skill checks, self-evaluation, peer review and progress board use and daily briefs to QIT were continued (Paper VI) (Figures 7 and 8).
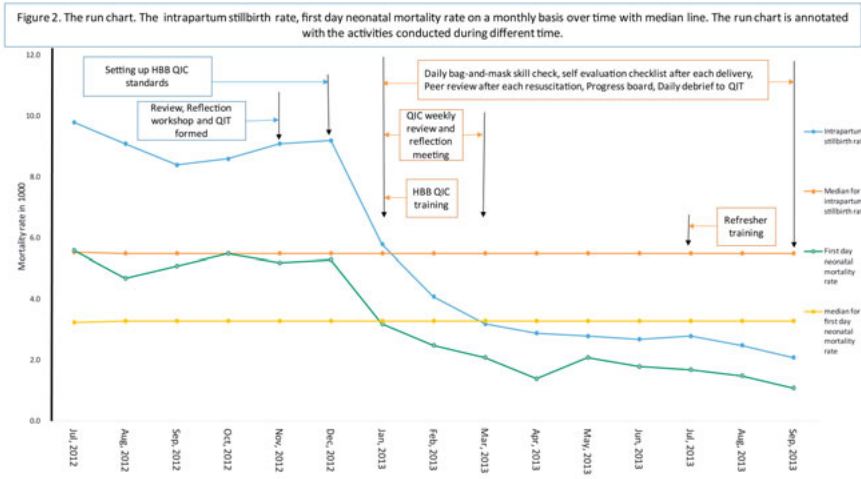
Figure 7. The run chart: The intrapartum stillbirth rate and first day neonatal mortality rate (with median) on a monthly basis over time. The run chart is annotated with the activities conducted during different time.
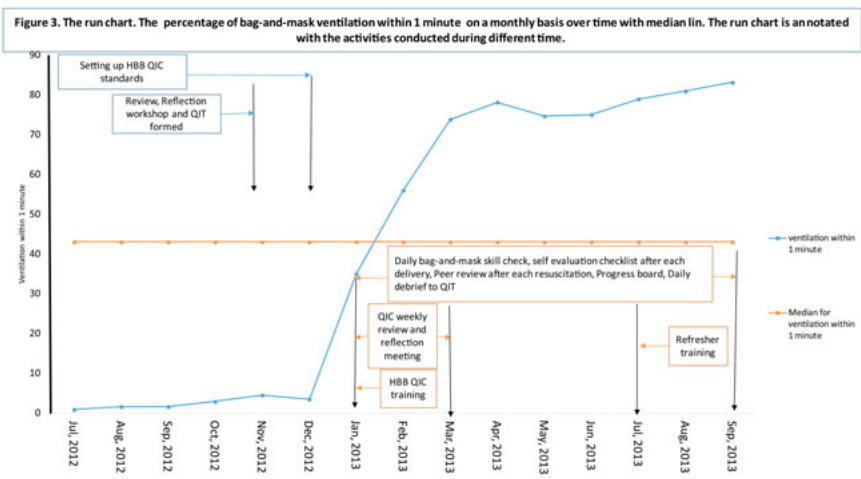
Figure 8. The run chart: The percentage of bag-and-mask ventilation within 1 minute (with median) on a monthly basis over time. The run chart is annotated with the activities conducted during different time.

On evaluation of the adherence of health workers to the neonatal resuscitation protocol before and after implementation of HBB QIC among the control population, 488 and 588 babies were resuscitated, respectively. The odds of performing stimulation or suction decreased by 62% (OR 0.38, 95% CI 0.29–0.49) and 87% (OR 0.13, 95% CI 0.09–0.17) respectively, after

HBB QIC implementation. The odds for bag-and-mask ventilation increased more than two times (OR 2.56, 95% CI 1.67–3.93). In the baseline period, none of the non-breathing babies (0/31) received bag-and-mask ventilation within one minute. In the intervention period, 83.9% (73/87) of the babies received ventilation within one minute.

During the study, perinatal mortality was lower in the intervention than in the baseline period (23.3 versus 30.9/1,000 deliveries). The intrapartum stillbirth rate was lower in the intervention period compared to baseline (3.2 versus 9.0/1,000 deliveries). The first-day mortality rate decreased from 5.2 to 1.9/1,000 live births from the baseline to the intervention period (Paper VI).

Multiple regression analysis was conducted to assess the change in outcome measures before and after implementation of HBB QIC. The analysis showed that the odds for intrapartum stillbirths decreased by 54% (aOR, 0.46, 95% CI 0.32–0.66), and for first-day neonatal mortality by 49% (aOR 0.51, 95% CI 0.31–0.83) after adjusting for ANC attendance and gestational age (Table 8). There was no change in overall perinatal death or stillbirth after adjusting for potential confounders (Paper VI).

Table 8. Risk of mortality outcomes before and after HBB intervention in the case-control population

	Adjusted Odds Ratio	95% CI	
		Lower	Upper
Perinatal mortality			
No	Ref		
Yes	1.03	0.84	1.25
Stillbirths			
No	Ref		
Yes	1.04	0.84	1.30
Intrapartum stillbirths			
No	Ref		
Yes	0.46	0.32	0.66
First-day mortality			
No	Ref		
Yes	0.51	0.31	0.83
Intrapartum-related deaths			
No	Ref		
Yes	0.47	0.35	0.63

In the next section, I will discuss the results of the thesis, along with the methodological considerations.

Discussion

This section of the thesis discusses the different risk factors for antepartum stillbirth; intrapartum stillbirth and neonatal death in a tertiary care setting as well as the comparison of the results to the similar findings from other studies conducted in low-income and middle-income settings. This section also provides an explanation for the change in the health workers' competency and performance scores for neonatal resuscitation before and after implementation of HBB QIC as well as the change in the mortality outcomes.

Risk factors for antepartum stillbirth and risk reduction strategy

The risk of antepartum stillbirth was higher among women with less than five years of education, who belonged to the poorest family, had higher parity and who did not attend any antenatal care visits. Similarly, the risk of antepartum stillbirth also increased for women who had a previous stillbirth, antepartum hemorrhage or hypertensive disorder during pregnancy, or small-for-gestational age babies in a tertiary hospital setting in Nepal. Similar to our results, studies in developed countries have identified several modifiable risk factors for antepartum stillbirth such as lack of antenatal care, antepartum hemorrhage, hypertensive disorder during pregnancy, and small-for-gestational age babies, however, the socio-economic and health service settings were different [22, 120, 121]. A study conducted in India has also identified lack of antenatal care as a modifiable risk factor for stillbirth [122].

There are possible explanations for the associations seen between some of these risk factors and antepartum stillbirth. For example, women with hypertensive disorder during pregnancy are more likely to have placental compromise, and thus a higher risk of fetal death. Additionally, women with increasing maternal age are more likely to have chronic hypertension and placental pathologies [123].

Studies have shown that antenatal care given by a skilled healthcare provider is a cost-effective intervention [124-126]. These visits provide a screening

opportunity for certain risk factors that are shown to be associated with antepartum hemorrhage, certain medical conditions, infection or hypertensive disorder [124-126]. If risks are detected, healthcare providers have the opportunity to immediately manage or treat specific conditions, or to establish a future care plan. Additionally, they can provide counseling to mothers and families, all of which can help to prevent antepartum stillbirth.

Currently, the Government of Nepal provides access to information on birth preparedness and the importance of antenatal care to women and their families through the community mobilization of community health workers and volunteers [127-130]. Auxiliary nurse midwives, nurses and doctors, provide the access to antenatal care through the mobile and static clinics [129]. The community mobilization of a cadre of health workers has been found to be an effective strategy to improving the knowledge and self-identification on the danger signs during pregnancy, as has early referral to a health facility, especially in the under-served areas where the risk of antepartum stillbirth is highest [127]. The community health workers require more support for increasing their access to families who are poor and uneducated for providing education and behavioral change interventions for care during pregnancy and early risk identification and referral. Implementation research is required to evaluate the community mobilization strategy, which can provide early detection of high-risk pregnancy and effective referral, and, ultimately, reduce antepartum stillbirth rate.

Risk factors for intrapartum stillbirth and strategy to prevent intrapartum stillbirth

This thesis revealed that the risk of intrapartum stillbirth was higher among women who had higher parity, had multiple pregnancies, antepartum hemorrhage and no antenatal care. Women who had obstetric complications during the intrapartum period, such as mal-presentation and prolonged labor, were more at risk of intrapartum stillbirth. Those women whose fetal heart rate was inadequately monitored and whose labor was not monitored using the partogram, had an increased risk of intrapartum stillbirth. Women who had a preterm birth, along with a fetus of small weight for gestational age, were found to have risk of intrapartum stillbirth. The risk of intrapartum stillbirth was found to be highest when there was a premature delivery combined with small weight for gestational age.

Similar to our findings, a study in Gambia by Ha et al showed that there is an increase in the risk of intrapartum stillbirth in women whose families are subjected to socio-economic deprivation, potentially because poorer women

receive sub-optimal antenatal care. These women may not have enough resources to afford the out-of-pocket expenses for screenings during pregnancy, or go to even travel to see a skilled care provider for antenatal checkups (ANC) [27].

ANC plays a vital role in the improvement of women's health during pregnancy, and women who lack access to antenatal checkups are at an increased risk of intrapartum stillbirth. Our results are consistent with other studies conducted in Gambia and Zimbabwe [29, 131]. ANC provided by a skilled provider can help women to better understand the growth and development requirements of a fetus and the support that it needs during this time, as well as to increase their attention to the importance of maintaining adequate health and nutritional status [132, 133]. Antenatal checkups also provide a platform for initiating a discussion with women on how to prepare for delivery, identify potential danger signs during pregnancy and labor, and understand when it is time to seek care because the delivery is imminent [134, 135]. Less educated women may have less access to information regarding birth preparedness and care seeking for any danger signs during pregnancy, which have been consistently identified as risk factors for intrapartum stillbirth both in high- and low-income countries [22, 30]. These aspects can also be addressed and corrected through discussion and teaching at ANC checkups.

Obstetric complications occurring during labor due to mal-presentation or prolonged labor can cause intrapartum insults to the fetus, thus leading to an intrapartum death [28, 136]. These deaths can be averted if better obstetric care and monitoring is available. In those settings where FHRM is sub-optimal and partogram is not used to monitor labor progression, the risk of death further increases [137].

Multiple births are associated with maternal morbidities, such as preterm labor and antepartum hemorrhage; the majority of twin pregnancies are associated with the delivery of SGA babies, and in some cases, multiple births can lead to death during the antepartum and intrapartum period [138-140]. Studies have shown that women with multiple pregnancies who receive adequate obstetric care during pregnancy and the intrapartum period, do not have adverse outcomes [141].

As shown in the findings from this study and several other studies, premature deliveries and babies who are SGA have the highest risk of intrapartum stillbirth, and the risk of death increases in very premature deliveries [22, 142, 143].

One of the new finding from this study is that the sub-optimal use of FHRM and the partogram for monitoring labor progress is associated with intrapartum stillbirth. A potential reason for this finding is that high-risk deliveries, such as those involving fetal distress, are not identified, which can lead to intrapartum insults to the fetus. Similarly, the appropriate interventions required to prevent prolonged labor, or other obstetric complications during labor due to mal-presentation or maternal medical condition, cannot be detected in a timely manner if a partogram is not used to monitor the progress of labor. These complications can lead to severe fetal compromise during the intrapartum period, and thus to intrapartum stillbirth, which could have been prevented in a tertiary care setting where emergency obstetric care is available.

Inadequate adherence to standardized protocols for intrapartum monitoring can be due to a multitude of factors. These factors could range from lack of health institution leadership and/or support to improve clinical practice, shortages of staff, poor knowledge on the use of the partogram or FHRM, heavy workload for an inadequate number of staff, to a lack of understanding of the relevance of the partogram in preventing obstructed labor as shown by studies in Africa [144-149]. Further exploration of possible contextual barriers to adherence to standard practices, and to identify possible interventions that help to facilitate adherence to standard protocols, is necessary.

Risk factors for neonatal death and strategy to prevent and manage risk factors

The third paper of the thesis has shown that neonates who are born from a less educated mother, whose mothers had previous pregnancies, and who had no antenatal care, had a greater risk of dying during the neonatal period. Women who had obstetric complications during the intrapartum period also had a risk of neonatal death. The risk of neonatal mortality in Nepal was highest among babies born both preterm and SGA, followed by babies born preterm, and then by SGA babies. Babies who are born prematurely or are SGA have an increased risk of hypothermia, infection, respiratory distress syndrome (RDS), intracranial hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, neurodevelopmental impairment and mortality [37, 40, 41]. These complications could potentially be prevented, or minimized, with interventions such as Kangaroo Mother Care and extra-support for feeding, case management of babies with signs of infection, safe oxygen management and supportive care for RDS, hospital care of babies with RDS,

use of continuous positive airway pressure (CPAP), and surfactant, or intensive neonatal care [42-45].

Methodological consideration on the analysis of risk factors for antepartum stillbirth, intrapartum stillbirth and neonatal death

Generalization

Because this was a hospital-based study, the background characteristics of women might be different at the population level. Although findings from hospital-based studies may have limited generalizability at the population level, the lack of a national periodic perinatal health surveys or a vital registration system in Nepal leaves hospital-based studies as one of the best options to identify burden of disease. The information produced by these studies is vital for the improvement of clinical practices, including intrapartum care, as well as the improvement of care at the community level, through the translation of best practice to these settings.

The population-based references for determining birth weight according to gestational age and sex were not available for the Nepali setting, so US population-based references were used.

This is a case-referent study, which can only demonstrate an association between the various risk factors with antepartum stillbirth, intrapartum stillbirth and neonatal death, but cannot determine the causal relationship.

Selection bias

There may have been data selectivity by the surveillance officers, either subconsciously or consciously, between the case and referent populations, as the outcome was known.

Performance bias

There may have been some potential bias within this study, such as failure of health workers to correctly assess maternal medical conditions during the clinical examination at admission. Some of the potential risk factors for antepartum stillbirth, such as placental insufficiency or genetic disorders, could not be assessed due to the lack of placental examination, both grossly and microscopically, and gene analysis. Not all women, even those who had

antenatal care, had screening for medical and/or obstetric complications during pregnancy, so there could be under-reporting of these conditions.

Information bias

There may have been information bias, where the health worker failed to record FHRM or use the partogram even if measurements were taken, which would be misclassified as the FHRM or the partogram not being completed.

Interviewer's bias

The telephone follow-ups were only completed for the referent population, so the neonatal deaths occurring in the non-referent population (80%) after discharge were missed, which could potentially result in the under-reporting of neonatal mortality due to prematurity or small for gestational age.

Change in the adherence to neonatal resuscitation and perinatal outcomes before and after implementation of HBB QIC.

Before the HBB QIC implementation, about half of the babies who did not require neonatal resuscitation (breathing/crying) were resuscitated. The adherence to using stimulation, suctioning and bag-and-mask ventilation for non-breathing babies was not adequate and none of these babies received initiation of resuscitation in the first minute of life.

The health workers were not competent in neonatal resuscitation skills before implementation of HBB QIC. After the HBB QIC implementation, 93% of the health workers were competent in resuscitation skills and these skills were retained until six months after training.

Various implementation strategies were applied as part of a HBB quality improvement cycle to improve the knowledge and competency at various points in time during the intervention period. The health workers who conducted bag-and-mask skill checks daily, made preparation for every birth, used the self-evaluation checklists after each delivery and attended the weekly review and reflection meetings had retention of their neonatal resuscitation skills even six month after the completion of training.

The implementation of an HBB QIC was associated with an improvement in the adherence of health workers' practice to neonatal resuscitation protocols, as well as a reduction in intrapartum stillbirth and first-day neonatal mortali-

ty. The study demonstrated the association of an HBB QIC with the decline in the over-use of suctioning and stimulation in babies who were breathing; as well as in those infants who were not breathing, for which the health worker moved more quickly to initiate bag-and-mask ventilation. This study provided, for the first time and by using video recordings, clear evidence on the improvement of health workers' performance. Bag-and-mask ventilation within the Golden Minute^{TM} increased by 84% from pre- to post-implementation. Most importantly, we demonstrated that a quality improvement approach to enhance neonatal resuscitation practices in a tertiary hospital is feasible and can result in substantial improvement in clinical outcomes.

Several studies in high-income and low-income countries have shown that resuscitation knowledge and skill improves immediately after the training, however, the resuscitation skills tend to deteriorate over a period of time [90-96]. Therefore, neonatal resuscitation training is in itself not an effective implementation strategy to retain resuscitation skills. Similar to our findings from this study, a study conducted in Canada has shown that a review of schematic posters on neonatal resuscitation before or after resuscitation of babies is not an effective strategy for the retention of neonatal skills [150].

Several systematic reviews have shown that review of the clinical performance among health workers on a periodic basis provides an opportunity to share the challenges faced in the clinical setting and improve the clinical skills and performance as a team, especially if the baseline skills and performance on a clinical protocol are poor [79, 80, 151, 152]. The study showed that conducting weekly review meetings among the nursing staff on the clinical performance on resuscitation can help to improve the resuscitation skills to a moderate extent as the baseline neonatal resuscitation competency was poor. Systematic reviews have also shown that a combination of educational strategies, such as weekly review meetings, and periodic simulated skill checks, checklists and self-evaluation is a more effective strategy to improve the clinical performance than a single strategy [81, 153-156]. However, these educational strategies were never implemented in combination to improve and retain the neonatal resuscitation skills in other studies.

There are several potential reasons that the improved adherence to neonatal resuscitation occurred using the HBB QIC approach.

First, the hospital leadership recognized the inadequate adherence to standard protocols within the hospital, and thus identified a need for change. Furthermore, the multi-disciplinary QIT, which included hospital staff members, was responsible for developing the quality improvement plan and con-

ducting daily debriefings of the HBB QIC implementation progress. There are several previous studies that have shown that leadership plays a crucial role in the quality improvement process [157, 158].

Second, the unit-based review on the root causes of poor performance of neonatal resuscitation and development of the quality improvement goals, objectives and standards, allowed the individual health workers to discuss their experiences and to be involved in the creation of the QIC. This process can create an environment that is conducive for implementing a quality improvement plan and for building teamwork [116, 159, 160].

Third, the introduction of self-evaluation checklists, in general, can improve compliance with best clinical practice [154].

And finally, the HBB QIC progress boards placed in each unit provided a constant reminder to the staff of the quality improvement effort. Displaying data on implementation progress at each nursing station, in each delivery unit, allowed for constant review and identification of potential problems in the implementation of the QIC, which has also been seen in other quality improvement studies [154, 159].

In the context of Nepal, the quality of neonatal resuscitation needs to improve from that of the current state by improving the health workers' performance on neonatal resuscitation [161, 162]. The birth attendants need to improve their competency in neonatal resuscitation skills and must sustain this competency such that knowledge is translated into clinical practice to reduce the burden of intrapartum-related death and morbidity. Nepal's current national strategy to provide skilled attendants at birth through training programs on neonatal resuscitation and seldom-clinical mentorship is not adequate to sustain the clinical competency on neonatal resuscitation, as shown by several studies [104, 106, 161, 163]. A combination of strategies is required ensure that each clinical competency after the training is retained and translated into clinical practice.

Methodological consideration for evaluation of HBB QIC

Similar to other published work on the use of CCD cameras as a method to evaluate neonatal resuscitation, this observational study found this technique to be useful for identifying deviations from protocol and areas for improvement [164-167].

There are, however, certain limitations to the study.

First, this is an observational study, thus the effectiveness of each component within the HBB QIC cannot be evaluated, and we can only derive the association between the intervention and the desired effects; however, causation cannot be established.

Second, a package of interventions made up the QIC, and thus we could not unbundle the package to demonstrate the association of individual interventions with the outcome.

Third, the use of self-evaluation checklists was evaluated based on whether the forms were completed correctly by the participants along with the other forms that had to be completed, so there could be some discrepancy between practice and what was actually recorded.

Fourth, attendance at the weekly review meetings on HBB QIC progress was assessed using the meeting notes and participant lists; however, the level of participation was not assessed.

Fifth, the quality improvement cycle was implemented on a unit basis, so there might be inter-cluster variation between the teams [168].

Finally, there may be measurement bias based on the inaccurate identification and/or documentation of an infant as stillborn rather than live-born with neonatal death, thus leading to differential misclassification of individual outcomes and exposures.

Conclusion

Based on the findings described in this thesis, the key conclusions are:

1. Antenatal Care is the preventable risk factor for antepartum stillbirth: Among the several risk factors identified, lack of antenatal care from a skilled provider has the highest risk for antepartum stillbirth (paper I).

2. Inadequate adherence to Fetal Heart Rate Monitoring and the use of partogram is the preventable risk factor for intrapartum stillbirth (paper II).

3. Preterm birth and small weight as per gestational age has the highest risk factor for neonatal mortality (paper III).

4. Care of the newborns at birth is inadequate and health workers trained as skilled birth attendants inadequately adhere to the standard neonatal resuscitation protocol (paper IV).

5. Health workers who practiced bag-and-mask skills, prepared for resuscitation before every birth, used self-evaluation checklists and attended weekly review meetings retained their neonatal resuscitation competency six months after the training (paper V).

6. A new approach for improving clinical performance for neonatal resuscitation using HBB QIC reduced intrapartum stillbirth and first-day neonatal mortality, as well as an increased adherence to the HBB protocol among health workers at a tertiary hospital (paper VI).

Recommendations

Policy and Programmatic recommendations

Among the various socio-demographic factors that are associated with antepartum stillbirth, lack of quality antenatal care is one of the major modifiable risk factors. As antepartum stillbirth occurs in the poorest families and in women who are less educated, improving the access to and quality antenatal care in the underserved population will help to screen and detect maternal morbidity and fetal growth. The community mobilization using the network of community health workers and volunteers should be strengthened to reach the underserved population, such that these high-risk mothers access antenatal care from a skilled provider.

To further improve the reduction in the intrapartum-related stillbirth, quality of intrapartum care is important. Despite the increase in the utilization of institutional delivery, the adherence to fetal heart rate monitoring and use of partogram to detect the progress of labor and fetal wellbeing is poor, even in a tertiary care setting in Nepal. The continuous quality improvement process to improve the health workers' competency and performance on intrapartum care should be part of the capacity development process.

To prevent the babies who are born premature and small for gestational from neonatal death, cost-effective interventions such as Kangaroo Mother Care should be strengthened at the hospital setting. More investment is required to improve the management of complications from prematurity by setting up special newborn care units and neonatal intensive care units.

Despite the existence of the standard protocol for neonatal resuscitation in a health facility setting, skilled providers do not adhere to the guidelines for neonatal resuscitation and there is a tendency for over-use of simple resuscitation techniques such as suctioning and stimulation along with inadequate use of bag and mask. Providing only standard neonatal resuscitation training to health providers is not adequate. A multi-faceted approach which includes strategies conducive to learning and an effective feedback environment in the delivery setting, such as preparation for every birth, daily bag-and-mask skill check, self-evaluation checklist and weekly review and reflection meetings, should be integral to the continuous quality improvement process in the hospitals. These clinical competencies coupled with regular re-evaluation, when translated to the clinical management of non-breathing babies will result in a reduction in intrapartum stillbirths and early neonatal mortality.

Recommendation for future research

- Can specific maternal complications during pregnancy and intrapartum period be used as a predictor to determine higher risk of antepartum stillbirth, intrapartum stillbirth, early neonatal death at an earlier stage?

- Demographic surveillance for improving methods for antepartum and intrapartum stillbirth rate measurement and risk factor analysis.

- Development research on evaluating the low-cost fetal heart rate monitor, which improves health workers' performance for intrapartum care.

- Implementation research on the educational approach, which can improve quality of care during labor and birth to reduce intrapartum stillbirths, neonatal mortality and disability.

- Implementation research on whether HBB QIC can improve the health workers' competency and performance in the primary care setting.

- Development research to create and develop new interventions and novel approaches to preventing preterm births.

- Implementation research on improving the health workers' performance on managing preterm babies.

Summary in English

In Nepal, there have been significant improvements in child health over the last 10 years, and further improvement in the reduction of the number of deaths in the first 28 days of life, the neonatal period, is needed. Furthermore, stillbirths account for a large burden of death in Nepal, but are largely invisible in society and health policy.

A research study was conducted at a tertiary level hospital in Nepal, Paropakar Maternity and Women's hospital, to identify risk factors for stillbirth occurring before and during labor, and risk factors for neonatal death. The study group evaluated an intervention to reduce the stillbirth and neonatal death. The intervention consisted of improving health workers' competency and performance on a simplified neonatal resuscitation protocol, Helping Babies Breathe (HBB). The study was conducted from July 2012 to September 2013.

The study found the family's socio-economic deprivation to be a risk factor for stillbirth and neonatal death. Similarly, uneducated mothers who were previously pregnant, who had no access to antenatal care, had obstetric complications during pregnancy and labor had higher risk of stillbirth and neonatal death. Further results show that women with small babies and prematurely born babies had the highest risk of death of their neonates. The health workers' adherence to neonatal resuscitation was poor before implementation of the HBB intervention in the hospital. After the implementation of the HBB neonatal resuscitation guidelines, the health workers' knowledge and skills in relation to resuscitation improved and there was an increased adherence to neonatal resuscitation. The study found that health workers who daily practiced skill checks on mannequins, prepared for neonatal resuscitation before every birth, used checklists for neonatal resuscitation and attended weekly review meetings retained their skills. The intrapartum stillbirth and neonatal mortality on the day of birth reduced by 50% after the implementation of the new neonatal resuscitation guidelines.

The HBB neonatal resuscitation guidelines need to be implemented in all the secondary and referral hospitals to further reduce the stillbirth and neonatal death rate in Nepal. More studies are required to evaluate the implementa-

tion of these new guidelines in birthing centers where most of the deliveries take place and where health workers have less support from clinical supervisors.

Summary in Nepali

विगत दश वर्षमा नेपालमा बाल स्वास्थ्यको क्षेत्रमा उल्लेख्य सुधार भएपनि नवजात शिशुहरुको स्वास्थ्यमा सो अनुसार प्रगति भएको छैन । मृत जन्म नेपाली समाजमा लुकेर रहेको र स्वास्थ्यको नीति र कार्यक्रम पनि ओभेलमा परेको छ र साथै नवजात शिशु मृत्युले बाल मृत्युको एउटा ठुलो हिस्सा ओगटेको छ ।

प्रसूति पूर्व र प्रसूतिको समयमा मृत जन्मको सम्भावित कारणहरु तथा नवजात शिशुको मृत्यु हुने सम्भावित कारणहरु पत्ता लगाउने उद्देश्यले परोपकार प्रसूति तथा स्त्रीरोग अस्पताल थपाथली, काठमांडौमा यो अध्ययन गरिएको थियो । अध्ययन समूहले सम्भावित कारणहरु पत्ता लगाएपश्चात मृत जन्म तथा नवजात शिशु मृत्यु घटाउने एउटा कार्यक्रमको मूल्याङ्कन गरेको थियो । उल्लेखित कार्यक्रमले स्वास्थ्यकर्मीको जन्मदा निस्साशिएको शिशुलाई व्यवस्थापन गर्ने सीप तथा क्षमतालाई अभिवृद्धि गर्ने उद्देश्य थियो । यो अध्ययन जुलाई २०१२ देखि सेप्टेम्बर २०१३ सम्म सञ्चालन गरिएको थियो ।

यस अध्ययन अनुसार कमजोर आर्थिक अवस्था भएका परिवारमा मृत जन्म तथा नवजात शिशु मृत्युको एउटा कारणको रुपमा देखिएको थियो । यसै गरी साक्षरता कम भएका आमा जो पहिले पनि गर्भवती भएकी थिइन, जसको पूर्व प्रसूति सेवामा पहुँच थिएन, जसलाई गर्भावस्था तथा प्रसूतिको समयमा गर्भसम्बन्धी जटिलता उत्पन्न भएको थियो त्यस्ता आमाबाट जन्मने शिशु मृत जन्मने तथा त्यस्ता आमाबाट जन्मिएका शिशुको नवजात अवस्थामा नै मृत्यु हुने खतरा बढी हुने पाइयो । त्यस्ता गर्भवती महिलाहरु जसको पेट भित्रको शिशुको मुटुको गती अनुगमन गरिएको थिएन र प्रसव पिडाको अनुगमन पार्टोग्रामको प्रयोग गरेर गरिएको थिएन त्यस्ता महिलाहरुबाट मृत शिशु जन्मने सम्भावना सबैभन्दा बढी भएको पाईयो । माथि उल्लेखित कार्यक्रम लागू हुनु भन्दा पहिले स्वास्थ्यकर्मीहरुमा जन्मदा निस्साशिएको शिशुको व्यवस्थापन गर्ने सीपमा कमी पाइयो । उक्त कार्यक्रमले स्वास्थ्य कर्मीहरुको जन्मदा निस्साशिएको शिशुको व्यवस्थापन गर्ने ज्ञान र सीपमा सुधार भएको पाइयो । शिशु श्वास प्रश्वास सहयोगी क्रियाकलाप लागू भएपश्चात मृत शिशुको जन्म तथा पहिलो दिनमा हुने नवजात शिशुको मृत्युमा ५० प्रतिशतले कमी भएको पाईयो ।

मृत जन्म तथा नवजात शिशु मृत्युलाई अभ्र घटाउनका लागि जन्मदा निस्साशिएको शिशुलाई व्यवस्थापन गर्ने कार्यक्रम अस्पतालहरुमा लागु गर्नु पर्ने देखिन्छ । ग्रामीण क्षेत्रमा शिशुहरुको जन्म बर्थिङ्ग सेन्टरहरुमा हुने र नवजात शिशुको मृत्युपनि गाउँ घरमा हुने हुँदा जन्मदा निस्साशिएको शिशुलाई व्यवस्थापन गर्ने कार्यक्रमको प्रभावकारीता अध्ययन बर्थिङ्ग सेन्टरहरुमा आवश्यक देखिन्छ ।

Summary in Swedish

Sammanfattning på svenska

I Nepal har barnhälsan förbättrats markant de senaste 10 åren. För att minska barndödligheten ytterligare behöver dock överlevnaden under de första 28 dagarna, den neonatala perioden, förbättras. Dessutom utgör dödfödda barn, s.k. stillbirths, en stor del av mortalitetsbördan i Nepal, men är trots detta ett osynligt problem både i samhället och inom hälsopolicy.

En forskningsstudie genomfördes vid ett regionsjukhus i Nepal, Paropakar Maternity and Women's Hospital i Kathmandu, för att identifiera riskfaktorer för mortalitet under graviditet, förlossning och den neonatala perioden. Forskargruppen utvärderade därefter en intervention som syftade till att minska den perinatala dödligheten. Interventionen bestod av ett utbildningspaket med syfte att förbättra vårdpersonalens kompetens och praxis runt förenklade riktlinjer för neonatal återupplivning – Helping Babies Breathe (HBB). Forskningsstudien genomfördes mellan juni 2012 och september 2013.

Resultaten visar att mödrar som är outbildad och som tidigare varit gravida, som kommer från ekonomiskt utsatta familjer, som inte haft tillgång till mödravård under graviditeten, och som har obstetriska komplikationer under förlossningen, har en förhöjd risk att få ett dödfött barn eller att barnet dör under den neonatala perioden. Vidare visade resultaten att små barn (SGA) och för tidigt födda barn hade högst risk för neonatal död. Hälsopersonalens följsamhet till rådande riktlinjer för neonatal återupplivning var låg innan interventionen (HBB) infördes på sjukhuset. Efter införandet av dessa förenklade riktlinjerna för neonatal återupplivning kunde ökad kunskap bland hälsopersonalen och bättre följsamhet till kliniska protokoll noteras. Barnadödligheten i samband med förlossning och den första levnadsdagen minskade med 50% efter införandet av de nya riktlinjerna. Studien fann vidare att hälsopersonal som dagligen övade på dockor, som förberedde neonatal återupplivning inför varje förlossning, som använde kom-ihåg listor och som deltog i veckomöten bevarade sina kunskaper och färdigheter bättre.

Införandet av förenklade rutiner för neonatal återupplivning (Helping Babies Breathe) måste implementeras på alla distrikts och regionsjukhus för att ytterligare förbättra barnaöverlevnaden i Nepal. Fler studier krävs för att utvärdera införandet av dessa förenklade neonatala återupplivningsrutiner vid de hälsoinrättningar där merparten av förlossningar sker och där hälsopersonalen har mindre stöd i sitt kliniska arbete.

Acknowledgements

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Editor: The Dean of the Faculty of Medicine

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