UPPSALA
UNIVERSITET

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1308

Surviving birth

Studies of a simplified neonatal resuscitation protocol in a low-income context using a mixed-methods approach

JOHAN WRAMMERT

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2017

ISSN 1651-6206
ISBN 978-91-554-9839-9
urn:nbn:se:uu:diva-316728

Dissertation presented at Uppsala University to be publicly examined in Auditorium Minus, Museum Gustavianum, Akademigatan 3, Uppsala, Friday, 28 April 2017 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Nalini Singhal (Department of Peadiatrics, University of Calgary).

Abstract
Wrammert, J. 2017. Surviving birth. Studies of a simplified neonatal resuscitation protocol in a low-income context using a mixed-methods approach. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1308. 73 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-554-9839-9.

United Nations has lately stated ambitious health targets for 2030 in the Sustainable Development Goal agenda, following the already achieved progress between 1990 and 2015 when the number of children dying before the age of five was reduced by more than half. However, the mortality reduction in the first month of life after birth has not kept the same pace. Furthermore, a large number of stillbirths have previously not been accounted for. The aim of this thesis was to evaluate the impact of clinical training in neonatal resuscitation, and to identify strategies for an effective implementation at a maternal health facility in Nepal.

Focus group discussions were used to explore the perceptions of teamwork among staff working closest to the infant at the facility. A prospective cohort study with nested referents was applied to determine effect on birth outcomes after an intervention with Helping Babies Breathe, a simplified protocol for neonatal resuscitation. Sustainability of the acquired skills after training was addressed by employing a quality improvement cycle. Video recordings of health workers performance were collected to analyse adherence to protocol.

Midwives described the need for universal protocols in neonatal resuscitation and management involvement in clinical audit and feedback. There was a reduction of intrapartum stillbirth (aOR 0.46, 95% CI 0.32–0.66) and neonatal mortality within 24 hours of life (aOR 0.51, 95% CI 0.31–0.83) after the intervention. Ventilation of infants increased (OR 2.56, 95% CI 1.67–3.93) and potentially harmful suctioning was reduced (OR 0.13, 95% CI 0.09–0.17). Neonatal death from intrapartum-related complications was reduced and preterm infants survived additional days in the neonatal period after the intervention. Low birth weight was not found to be a predictor of deferred resuscitation in the studied context.

This study confirmed the robustness of Helping Babies Breathe as an educational tool for training in neonatal resuscitation. Accompanied with a quality improvement cycle it reduced intrapartum stillbirth and mortality on the day of delivery in a low-income facility setting. Improved postnatal care is needed to maintain the gains in survival through the neonatal period. Increased management involvement in audit and quality of care could improve clinical performance among health workers.

Keywords: cause of death, focus group, guideline adherence, infant, low-income population, low birth weight, Nepal, neonatal resuscitation, nurse midwives, neonatal mortality, newborn, perinatal mortality, preterm, quality improvement cycle, teamwork, postnatal, video recording

Johan Wrammert, Department of Women's and Children's Health, International Maternal and Child Health (IMCH), Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

ISSN 1651-6206
ISBN 978-91-554-9839-9
urn:nbn:se:uu:diva-316728 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-316728)

‘You cannot get the truth by capturing it, only by its capturing you’

Kierkegaard, 1850

To the children who lost their
lives in the Gorkha earthquake

Populärvetenskaplig sammanfattning

Från 1990 till 2015 minskade den globala barnadödligheten från 12.7 till 5.9 miljoner. Denna fantastiska utveckling är ett resultat av olika åtgärder som införts för att minska förekomsten av de vanligaste sjukdomarna under barnets fem första levnadsår. Dödsfall hos spädbarn under den första levnadsmånaden har tyvärr inte minskat i samma takt och andelen barn som dör under den neonatala perioden har därför ökat. Dessutom har minskningen av dödfödda barn skett i en långsammare takt. Tillsammans uppgår dödsfall hos barn under senare delen av graviditeten, i samband med förlossningen eller under den första levnadsmånaden till 5.5 miljoner per år. Majoriteten av dem (99 %) sker i låg- och medelinkomstländer. De flesta av de dödsfall som sker runt tiden för födelsen kan förhindras med billiga och enkla åtgärder. Det handlar om förbättrad mödravård, bättre fosterövervakning under förlossningen, att förlossningen sker under rena förhållanden, att tidig amning initieras och nedkylning av barnet förhindras samt upptäckt och behandling av infektioner. Ungefär en tiondel av alla barn som föds varje år behöver någon form av stöd för att komma igång med sin egen andning. De steg som då behöver användas kallas neonatal återupplivning, eller neonatal hjärt-lungräddning. Insatserna som behövs för flertalet av de barn som inte spontant börjar andas är också relativt enkla till sin natur. Det kan räcka med att torka av barnet eller stimulera huden med handflatan. En del behöver hjälp med sina första andetag genom att man blåser in luft i lungorna med hjälp av en mask. En mycket liten andel av barn som inte spontant börjar andas efter födseln behöver avancerade åtgärder såsom kompressioner av bröstkorgen, tillförsel av läkemedel eller respiratorbehandling.

I den här avhandlingen beskrivs en studie genomförd vid ett förlossningssjukhus i Kathmandu, Nepal. Vi genomförde en träningsinsats med ett förenklat program för neonatal återupplivning som kallas Helping Babies Breathe. Programmet är utvecklat av det amerikanska barnläkarförbundet och är anpassat för att användas i resurssvaga miljöer, såsom Nepal. Förutom utbildningsmaterial med bilder så inkluderar metoden även simulerad träning med en docka på vilken de olika stegen vid återupplivning utförs. All personal på sjukhuset, som har 22,000 förlossningar per år, tränades enligt programmet. Vi samlade samtidigt in information om hur det gick för barnen som föddes före, respektive efter, träningsinsatsen. Det är tidigare känt att förmågan att upprätthålla kunskaper efter klinisk träning kan vara ett pro-

blem. Med anledning av det åtföljdes träningen av ett antal kvalitetsfrämjande åtgärder syftande till att öka uthålligheten av förbättrad praxis. Barn som dog under förlossningsarbetet minskade med 54 % och antalet barn som avled inom de första 24 timmarna minskade med 49 % efter träningsinsatsen. Barn som föddes levande eller återupplivades framgångsrikt överlevde fler dagar efter träningen, men risken för nyfödda att dö senare under den första levnadsmånaden var oförändrad. Helping Babies Breathe var således ett lämpligt program för att minska dödsfall bland barn med förlossningsrelaterade komplikationer eller tidiga dödsfall efter födelsen. Förbättrat omhändertagande av nyfödda under de första levnadsveckorna krävs för att ytterligare minska dödligheten under nyföddhetsperioden på förlossningssjukhus i Nepal och i liknande resurssvaga miljöer.

List of Papers

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

I Wrammert, J., Devkota, S., Baral, K., KC, A., Målqvist, M., Larsson, M. Teamwork among midwives during neonatal resuscitation at a maternity hospital in Nepal. *Women & Birth, Article in press,* 2017

II KC, A., Wrammert, J., Clark, RB., Ewald, U., et al. Reducing perinatal mortality in Nepal using Helping Babies Breathe. *Pediatrics*, 2016:137(6)

III Wrammert, J., KC, A., Ewald, U., Målqvist, M. Improved postnatal care is needed to maintain gains in neonatal survival after the implementation of the Helping Babies Breathe initiative. *Accepted for publication in Acta Paediatrica*

IV Wrammert, J., Zetterlund, C., KC, A., Ewald, U., Målqvist, M. Resuscitation practices of low and normal birth weight infants in Nepal: an observational study using video camera recordings. *Submitted*

Contents

Abbreviations

ANC	Antenatal Care
aOR	Adjusted Odds Ratio
CI	Confidence Interval
HBB	Helping Babies Breathe
HBS	Helping babies Survive
KMC	Kangaroo Mother Care
LBW	Low Birth Weight
MDG	Millennium Development Goal
NBW	Normal Birth Weight
NICU	Neonatal Intensive Care Unit
QIC	Quality Improvement Cycle
QIT	Quality Improvement Team
WHO	World Health Organization
YLL	Years of Life Lost

Glossary

Perinatal mortality: deaths that occur from the time of a viable fetus at 22 weeks of gestation or with a birth weight of more than 500 grams until the first week after birth
Stillbirth: birth of a viable fetus from 22 weeks of gestation or with a birth weight of more than 500 grams with an Apgar score of zero at one and five minutes
Antepartum stillbirth: birth of a viable fetus from 22 weeks of gestation or with a birth weight of more than 500 grams, with an Apgar score of zero at one and five minutes, with signs of maceration, and no fetal heart rate detected at admission or at the onset of labor
Intrapartum stillbirth: birth of a viable fetus from 22 weeks of gestation or with a birth weight of more than 500 grams, with an Apgar score of zero at one and five minutes, with no signs of maceration, and where fetal heart rate was detected at admission or at the onset of labor
First-day neonatal mortality: death of a live-born infant within 24 hours after birth
Early neonatal mortality: death of a live-born infant within seven days of life
Late neonatal mortality: death of a live-born infant between seven and 27 days of life
Neonatal mortality: death of a live born infant within 27 days of life
Antenatal care attendance: whether a mother attended one or more visits to a health worker for medical examination and counseling during pregnancy
Gestational age: number of intrauterine weeks of a fetus calculated from the mothers last menstrual period
Low birth weight: birth weight below 2,500 grams
Preterm birth: infants born before 37 completed weeks of gestation
Term birth: infants born at or after 37 completed weeks of gestation
Very preterm birth: infants born before 32 completed weeks of gestation
Extremely preterm birth: infants born before 28 completed weeks of gestation
Teamwork: the process of working collaboratively in a group of two of more in order to achieve a common goal
Low-income country: countries with a gross national income per capita below 1,025 US dollars (2015)

Preface

Where I come from, losing a child at birth is to most parents a most incomprehensible thing. Something they have not really considered. Why? Pregnancy and childbirth in Sweden is safe. Quality of care for both mothers and newborn infants is among the better on the planet, if not the best. Having a child in my country is depicted as a joyful adventure in glossy magazines, where we learn what cart to chose, or why ecological cotton is better. Meanwhile, every sixth second, a newborn life is lost around the globe. Why? Pregnancy and childbirth in many parts of the world is *not* safe. The location of your birth determines your odds of survival. When I first came to Nepal, I was surprised by the attitude of people to the chances of survival of infants compared to mothers. If a mother would pass during pregnancy or childbirth, there were articles in the local press; there were meetings at the hospital and possibly protests outside the facility by family members. The crowd was demanding answers and looking for accountability. But infants passed by the numbers inside without any notice. As if all those lives never lived were unseen. I later realized it was a strategy of self-protection. Mothers, fathers and families just don't count on leaving the maternal facility with a new member until they actually pass out through the doors. Most people in Nepal know somebody who lost an infant during pregnancy and childbirth. So why should I be lucky? Better to prepare for the worst and hope for the best. The majority of these deaths can be prevented with cheap and simple things. The world has the knowledge of what those things are, and we certainly have the money to pay for them. What remains is *how* we should do it, and I hope this thesis provides some answers.

Johan Wrammert
March 2017
Uppsala

Introduction

Since the launch of the Millennium Development Goals (MDG) in 2001 there has been much progress in promoting child health and reducing child mortality [1]. From 1990 to 2015, child deaths before the age of five years were reduced from 12.7 to 5.9 million. A reduction was materialised in all regions of the world, but low- and income countries still account for 99% of all child deaths [2]. Although not reaching the MDG target of a reduction by two-thirds, the achievements cannot be underestimated. However, the reduction of stillbirths and neonatal deaths has been slower over the last 25 years, emphasizing the need to focus on the time surrounding birth going forward [3]. In global calls to further reduce the rates of stillbirths and neonatal deaths but also the closely linked burden of maternal mortality, the international community has launched many collaborative efforts during the last 5 years. A Promise Renewed and Every Newborn Action Plan address the preventable causes of these deaths, promoting universal coverage of basic life saving interventions for all mothers and newborn infants globally [4, 5]. The United Nations, through the Sustainable Development Goals (SDG), in 2015 also stipulated new ambitious targets: by 2030, child mortality and neonatal mortality in all countries should not exceed 25 and 12 deaths per 1,000 live births, respectively [6].

Perinatal mortality

The perinatal period stretches from the time of a viable fetus at 22 completed weeks of gestation until the first week after birth [7]. This is a period of time when both the mother and the child are at the highest risk of both mortality and morbidity. The progress during the last decades in reducing both maternal and child deaths can partly be explained by the increased focus on this strong link between maternal and child survival [8]. Addressing continuum of care, and increasing coverage of skilled health care attendance, from pregnancy, during childbirth and trough the postnatal period has been successful in reducing both maternal and perinatal mortality. Approximately 55 million people die each year on our planet from various causes, many of them preventable. Some might therefore argue why such focus should be directed at the perinatal period, as it is such a short period of life. A different way to describe the burden of disease is to use years of life lost (YLL). This

definition includes the burden of premature death due to different disorders during life. In 2005, a total of almost 1 billion years of life were lost by this definition and of them, one tenth originated from stillbirth (Table 1).

Table 1. *Years of life lost (YLL) from stillbirth and for the top five disorders globally in 2005 [9]*

Disorder	Years of life lost (1,000)
Stillbirth	99,592
Malignant neoplasms	95,928
Respiratory infections	83,068
Ischemic heart disease	79,412
Unintended accidents	78,330
Neonatal conditions	76,627

This proportion exceeds all other individual disorders of, for example, malignancy, respiratory infections, and ischemic heart disease [9]. Moreover, if YLL from complications of live born infants leading to premature death, such as low birth weight (LBW) and intrapartum hypoxia, are added, stillbirth and complications of birth accounted for more than 17% of all YLL in 2005 [10].

Stillbirth

A large number of lives are thus lost before life. The reports and definitions of stillbirth vary between countries as different cut-offs for gestational age and birth weight are used. In combination with the exclusion of stillborn infants from the MDG agenda, these deaths have previously been left behind and not prioritized [11]. Recent studies estimate that, according to the WHO definition of a baby born with no signs of life at or after 28 weeks of gestation or weighing 1,000 grams or more, 2.6 million infants were stillborn in 2015. Although lagging behind, the global burden of stillbirth was reduced by 19% between 2000 and 2015 [12]. More than half of the stillbirths (1.4 million) are antepartum stillbirths, lost before the onset of labor with the remaining deaths occurring in the intrapartum period due to complications during labor and birth [13]. The proportions of intrapartum stillbirths are higher in low-income countries and highest in south Asia where they constitute 54% of all stillbirths [14]. Risk factors for intrapartum stillbirth in low-income countries are among others: lack of antenatal care and skilled care at birth, absence of partogram use during labor, fetal growth restriction and prematurity, high maternal age and multi parity, and hypertensive disorders during pregnancy [13, 15].

Neonatal mortality

In addition to the estimated number of stillbirths every year, there are 2.9 million neonatal deaths occurring during the first four weeks of life [3]. Three-quarters of neonatal deaths occur in the first week with the highest risk of death on the very first day of life (Figure 1). The proportion of mortality in the first 24 hours of life is consistent across different settings [16].

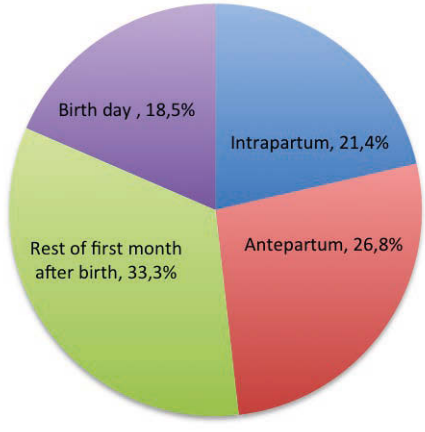

Figure 1. Global proportions of 5.5 million stillbirths and neonatal deaths [3]

As the reduction of neonatal mortality under the MDG agenda progressed about 30% slower than child mortality, neonatal health and survival is now higher on national agendas [17]. The focus going forward will be on targeting the three leading causes of neonatal death: complications from preterm birth, intrapartum-related complications (previously called birth asphyxia) and severe neonatal infection (Figure 2).

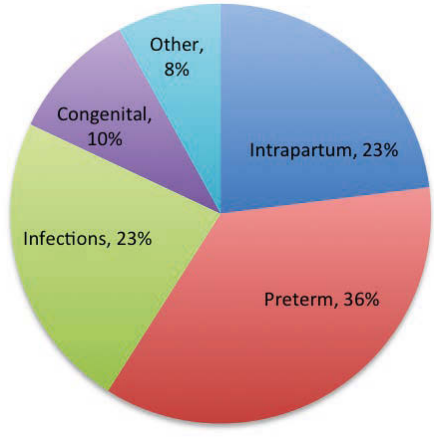

Figure 2. Primary causes of 2.9 million neonatal deaths globally [3]

Complications of preterm birth is the overall leading cause during the neonatal period but even more so during the early neonatal period (day 0-6) where 41% of the deaths are attributable to prematurity. Proportions are similar over different contexts, but the cause-specific risk is much higher in low-income countries, reflecting the low quality of postnatal care for premature infants in high mortality settings. During the late neonatal period (day 7-27), severe infection is the leading cause, responsible for 37% of deaths. Neonatal death from intrapartum-related complications was reduced by a third from 2000-2012, probably reflecting the increased rate of facility delivery as opposed to home delivery [18]. However, clearly linked to intrapartum-related neonatal deaths are intrapartum stillbirths, where death is assumed to have occurred before birth but where misclassification errors can occur as described later in this section. Finally, congenital malformations account for 10% of neonatal mortality globally. As diagnostics are improving, especially regarding cardiac malformations, proportions are rising to include mortality among infants previously misclassified as pneumonia deaths [19].

Morbidity

Neonatal survival might have consequences later in life. Neonatal encephalopathy is a complication following intrapartum hypoxic events that manifests in difficulties of respiration and neurological symptoms such as abnormal reflexes, muscle tone and seizures during the neonatal period [20]. It is graded as mild, moderate or severe where mild cases without symptoms after the first week of life rarely develop long-term morbidity whereas survivors of severe cases suffer life-long morbidity such as cerebral palsy [21]. As many as one million survivors of intrapartum-related events might develop neurological impairments but the lack of quality data from low-income contexts, especially community settings, make estimations difficult [22]. Morbidity attributed to preterm birth includes neurodevelopment complications among 354,000 survivors but also visual impairment of 185,000 infants following retinopathy of prematurity [23]. Premature infants are also more at risk for other neonatal complications, such as neonatal infection, hyperbilirubinaemia and feeding difficulties [24]. The risk for morbidity among all complications during delivery and the neonatal period is highly correlated to where the baby is born. In high-income and low-mortality regions few term and only 20% of preterm infants develop disability whereas as many as 7 million survivors born in regions with higher neonatal mortality are affected by life-threatening complications during birth and the postnatal period [25]. Impairment is most common in middle-income settings where the coverage of neonatal intensive care is improving but with still low quality. In settings with the highest rates of neonatal mortality, extremely premature infants with the highest risk of long-term disability rarely survive [23].

Stillbirth and live birth overlap

Following the efforts to distinguish the closely linked mortality from intrapartum-related stillbirths and intrapartum-related neonatal deaths, the question of potential misclassification of such deaths in low-income settings has been discussed [26]. In a setting where baseline resuscitation skills are low and where monitoring of vital signs are inadequate, a depressed live born infant could be inappropriately classified as a stillbirth if left unattended after birth [27]. With an increased proportion of survivors from intrapartum hypoxia following the introduction of basic newborn interventions, infants previously defined as stillborn are to a larger degree resuscitated [28]. However, when resources are poor, there is usually a need to prioritize. Infants born with low gestational age, LBW or with apparent congenital malformations might increase the risk that health workers defer resuscitation of an apneic infant and instead register a stillbirth (Figure 3) [29].

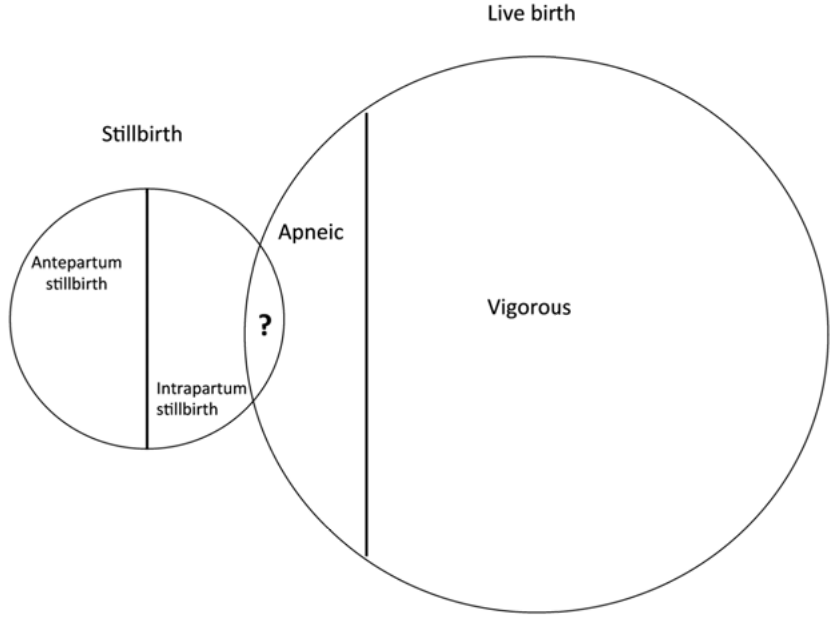

Figure 3. Stillbirth and live birth overlap. An apneic live born who is not resuscitated or for whom resuscitation is not available might be registered as a stillbirth

The anticipation that withholding resuscitation could spare staff from blame, or save the family from unacceptable costs of neonatal care or future disability, could also play a role if the chance of survival is taken as low [25]. Gender could also affect the decisions in such situations. Males actually run a higher risk of neonatal complications, but the different value attributed to sons and daughters by the prevailing social context could also play a role [30, 31]. The scope of errors in misclassification of stillbirths could be

greater in the still high number of home births in many low-income settings, where available data is scarce. The significant reduction of stillbirth rates from intervention studies performed in such settings also indicate effective resuscitation of infants after intervention, infants that were previously classified as stillbirths [32].

Interventions for increased neonatal survival

The introduction of the MDG number four addressing child mortality, and especially its attached measurable targets, inspired the global community of governments, researchers, medical specialists and donor organizations to an unprecedented level of engagement to improve child health and survival [33]. The knowledge of low-cost, and evidence-based interventions to reduce mortality around the time of birth followed. In a pivotal publication from 2005, Darmstadt et al demonstrated how universal coverage by a number of health interventions during pregnancy and birth could avert up to 70 % of all neonatal deaths globally at a low cost [34]. Out of the 16 interventions identified as supported by robust evidence for neonatal mortality reduction, 10 targeted the intrapartum and postnatal period. All of them are basic interventions possible to implement in most settings such as: injectable corticosteroids for mothers in preterm labor, labor surveillance using a partogram to early detect complications, clean delivery practices, promotion of early breast-feeding, kangaroo mother care (KMC) for LBW infants, neonatal infection detection and management, and resuscitation of non-breathing newborn infants.

Neonatal resuscitation

Early initiation of respiration is essential for the infant after leaving the intra-uterine life where all oxygenation has been supplied by the umbilical cord. The first breath we take in life will start a rapid transition to air-filled lungs as we overcome the frictional resistance of airway liquid and the surface tension at the air-liquid interface [35]. Most newborn infants perform this important transition spontaneously, whereas about 10 of the 130 million infants born every year require some assistance. Neonatal resuscitation is primarily of a basic nature. Most infants will respond to drying with a cloth after birth to initiate breathing. Some will need additional stimulation provided by rubbing the back of the infant and approximately 6 million will require support with positive pressure ventilation provided with a bag and mask (Figure 4). Which infants should then be resuscitated? The International Liaison Committee on Resuscitation states that this decision should be based on a combination of signs: crying, breathing, muscle tone, heart rate, maturity, and response to stimulation [36]. This initial assessment requires a

high level of skill. The WHO guide, on the other hand, recommends a more simple approach. All infants that do not cry; do not breathe at all; or who are gasping at 30 seconds after birth should be ventilated with a bag-and-mask [37].

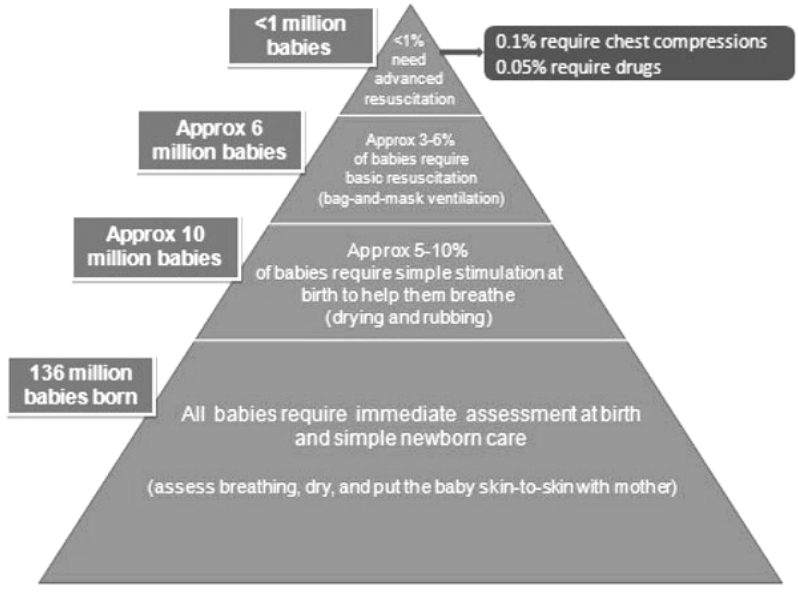

Figure 4. The need for various interventions during neonatal resuscitation [28]

Also infants suffering secondary apnea from a prolonged hypoxia during delivery will in most cases respond to ventilation as the bradycardia usually is secondary to respiratory failure [38]. Less than one percent of infants will need advanced resuscitation, including intubation, chest compression and administration of drugs, e.g. injections of adrenaline and provision of oxygen.

The role of suctioning of the airways has been widely used in neonatal resuscitation but it has lately been refuted as especially suctioning of the lower airways can harm the infant, causing injury or reflective bradycardia. In international guidelines for 2015, suctioning of the airways is no longer recommended in any situation other than when there is an apparent obstruction of the airway [39]. Administration of oxygen is another part of neonatal resuscitation under debate. There is no evidence to support initiation of resuscitation with 100% oxygen compared to room air and for premature infants high levels of oxygen might even be harmful [40]. If used, oxygen should be titrated according to the oxygen saturation levels of the infant and as medical gas blenders, and even oxymeters, are not always available in low-income settings, oxygen administration should not be a priority [41].

Several studies on training in neonatal resuscitation in low-income settings have demonstrated a reduction of intrapartum-related death. As randomization to such a study would be unethical, most studies are observational. In a large meta-analysis of facility-based studies available, and also using an expert Delphi panel, it was concluded that full coverage of this basic intervention in facilities worldwide could reduce mortality from intrapartum-related events by 30% [28].

Helping Babies Breathe

In a response to the available evidence supporting universal coverage of neonatal resuscitation skills in low-income settings, the American Academy of Pediatrics developed Helping Babies Breathe (HBB) [42]. This is an educational package consisting of context-adjusted pictorial flip charts, a learner workbook, a mannequin, and equipment of bag, mask and a bulb suction device. The protocol used is based on evidence from international guidelines [43]. The protocol is simplified in comparison to, for example, the National Resuscitation Protocol, focusing on the basic interventions of assessment, drying, stimulating, clearing the airway and initiating ventilation (Figure 5). 'The Golden Minute™' concept where ventilation should be started within 60 seconds on a non-breathing infant, emphasizes the key element of ventilation, should the infant not establish breathing spontaneously [44]. HBB has been evaluated in several studies, both for the effect on mortality outcomes and the development of skills. In an evaluation in Tanzania, HBB training reduced intrapartum stillbirth by 24% and neonatal death within 24 hours by 47% [45]. A study in India demonstrated a reduction of intrapartum stillbirth by 46% with unchanged neonatal mortality, suggesting resuscitated infants survived the neonatal period [46]. The educational package of HBB has also been tested for its effectiveness as a tool for training in low-income settings. In a study performed in Ethiopia, the HBB protocol was feasible for implementation and it improved knowledge and skills of neonatal resuscitation among health workers [47].

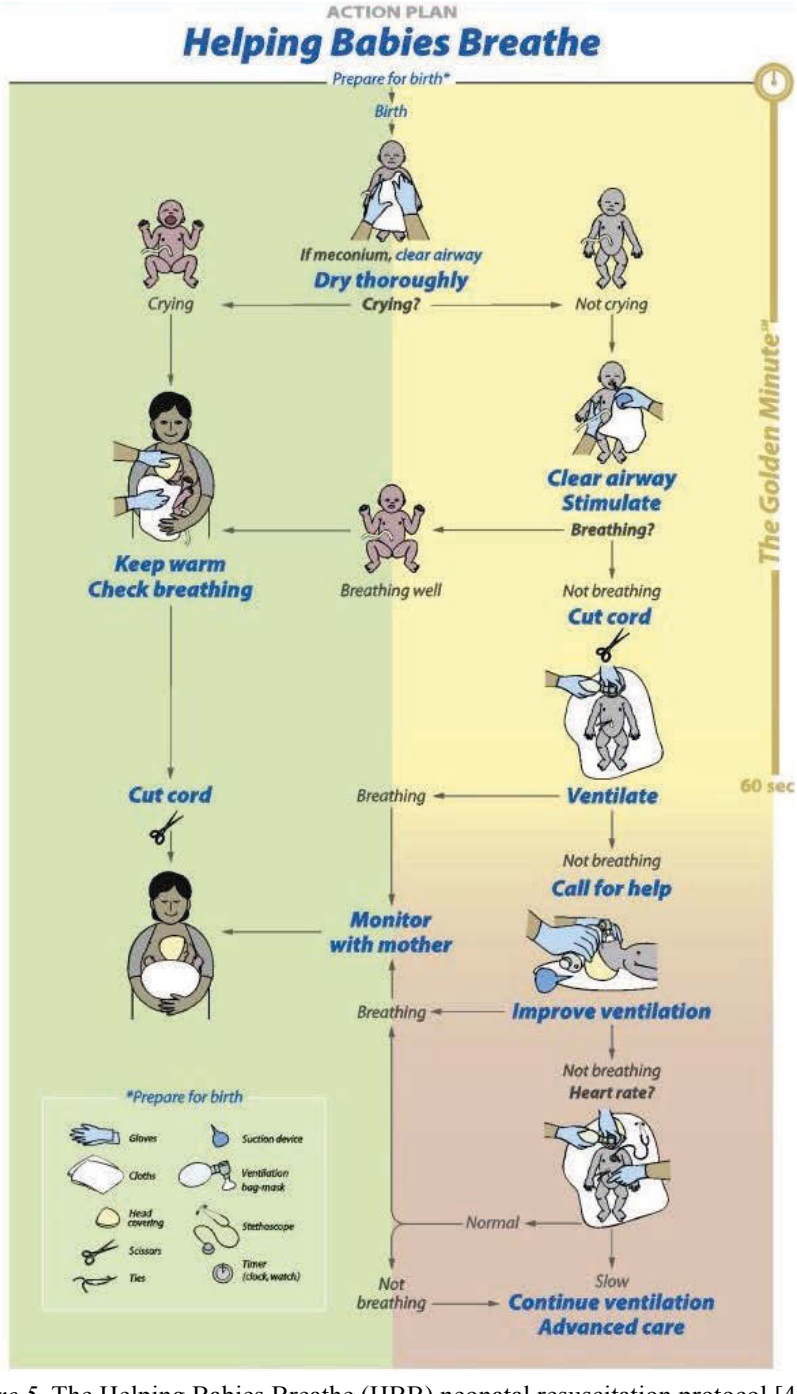

Figure 5. The Helping Babies Breathe (HBB) neonatal resuscitation protocol [48]

Ethics of neonatal resuscitation

As basic neonatal interventions such as HBB at facilities result in more survivors, ethical considerations might be raised [49]. The decision not to resuscitate immature infants in low-income settings may seem logical as extremely and very premature infants (<32 weeks) have lower odds of survival in such a setting [50]. However, historical leaps taken for neonatal survival in high-income settings has been demonstrated to follow a pattern of more survivors with unchanged morbidity requiring follow-up investment in postnatal care to subsequently decrease neonatal mortality (22). Pre-term babies with extremely low gestational age have driven the quality of neonatal care in high-income countries, but those babies rarely survive in settings with a baseline of high neonatal mortality. But, 85% of all pre-term births are moderate pre-terms and therefore account for most of the potentially impaired survivors. As there is considerably less morbidity in this group, the resuscitation and treatment of moderate pre-term infants should not be deferred because of the risk of long-term disability when basic postnatal care is available (23). Evidence of changes in long-term morbidity following training in neonatal resuscitation in low-income settings is scarce and remains a critical research question. Improved skills will most certainly prevent many hypoxic events and thus morbidity, but there are also concerns that those vulnerable survivors will develop disabilities [51]. Results from the few existing long-term follow-up studies in low-income settings do not clearly show an increased rate of morbidity after training in neonatal resuscitation, supporting the universal use of resuscitation for all infants who do not initiate breathing after birth regardless of gestational age and birth weight [28].

Knowledge translation

Even though several evidence-based interventions to improve health care outcome are available, health workers often fail to perform according to established guidelines [52]. This is also true for the performance of interventions aimed at reducing neonatal deaths [53]. This is not a problem isolated to low- and middle-income regions, and it has gained more attention the last decades. Also in high-income countries the simple steps in an evidence-based protocol for neonatal resuscitation is not always followed [54]. Understanding the critical determinants of performance and accordingly developing specific interventions will be crucial to achieve quality delivery of health care services [55]. Regarding neonatal resuscitation and the retention of acquired skills after training, a study of HBB in Rwanda revealed that the competency dropped to an unsatisfactory level three months after training, indicating that training alone was not enough for a long-term improvement in clinical performance [56]. A number of other studies performed in differ-

ent settings confirm this problem of knowledge retention following training in neonatal resuscitation [57-60].

Implementation strategies

The challenge of turning evidence-based interventions into sustainable change in clinical practice has inspired the growing field of implementation research [61]. Addressing this "know-do" gap in newborn care is of crucial importance in low-income settings as most of the mortality and morbidity stem from such settings [62]. Understanding contextual factors and tailoring interventions to bridge the gap has attained increased attention when targeting improved quality of care in complex health systems [63, 64]. In a response to knowledge translation issues, the Promoting Actions on Research Implementation in Health Services (PARiHS) framework highlight three crucial cornerstones: strong evidence, supportive organizational context, and appropriate facilitation [65]. Culture, leadership and evaluation are important factors to consider within the concept of context. Culture in an organization can simply be described as "the way we do things". More specifically, its stance on: values and beliefs, authority, response to organizational problems, interpersonal relationships, rewards, and teamwork [66]. As training alone to improve adherence to clinical guidelines does not seem to be sufficient, educational strategies have been developed [67]. A Cochrane report on effectiveness of implementation strategies in healthcare reported that educational meetings together with interactive sessions have the potential to change behaviour in complex clinical situations [68]. Such repetitive meetings and interactive sessions could be packaged into a quality improvement cycle (QIC), be implemented together with the neonatal resuscitation training, and kept in place for continuous re-training and management involvement.

Importance of teamwork

The midwife or birth attendant working closest with the mother and her newborn infant is central to determining the quality of care that is provided, and thus the outcome in neonatal resuscitation [69]. In order to evaluate what occurs on the resuscitation table, quantitative methods can be used to measure, for example, time to intervention, oxygen saturation levels, Apgar scores and mortality outcomes. However, the personal experiences of the staff involved as well as various group dynamics will also affect the steps taken to resuscitate the infant. To understand these contextual factors, there is a need for qualitative studies to complement quantitative measures. In this area very little data is available from low-income settings [70]. The importance of teamwork in newborn care has been studied before but mainly in high-income settings. Focus group discussions with staff from a neonatal

ward in the USA found that provider characteristics, such as personality, reputation and expertise as well as organization and working environment, are important for a well-functioning team [71]. Another study from a neonatal facility in south-central USA proposed that professional attitudes, maintaining relationships and having concurrence about the team's goal are factors that influence teamwork [72]. Finally, reviewing the little qualitative data available from low-income settings, literature suggests other specific barriers that can affect the quality of care for newborn infants. A study in Malawi demonstrated that knowledge and experience was in place, but the lack of equipment and universal protocols along with ethical considerations could form barriers for health workers to apply neonatal resuscitation [73].

Evaluation of resuscitation practices

The immediate care for respiratory depressed infants is a stressed and often-chaotic situation in any setting, and a better understanding of what is actually going on at the resuscitation table is in demand [74]. Within the PARiHS framework, evaluation is also referred to as an important part of the contextual aspect, as it can be used to provide feedback and improve organizational learning. PARiHS also emphasizes that effective health care systems should take the opportunity to use multiple sources of evidence for evaluation [66]. Quantitative observational methods can be used to measure the initiation and timing of different interventions, but lacks reliability when classical data collection tools, such as manual registration of events or retrospective reviews of medical records, are used [75]. Methods using video camera surveillance have therefore emerged as a promising way of investigating performance and adherence to clinical protocols in resuscitation. The first attempt in an adult setting was performed as long back as 1969, but it was not utilized in evaluating neonatal resuscitation until 2000 [76, 77]. Authors of the studies that have followed, found it to be a feasible method for quality assessment and to increase the level of teamwork, leadership and communication within a resuscitation workgroup [54, 77]. However, when analyzing video manually, issues of intra- and interobserver variability are introduced, and for large cohorts the analysis is time consuming [54, 78]. Collecting data from video recordings using image processing or recent advances in deep learning action classification could be an alternative [79].

Newborn health in Nepal

Nepal is a low-income country situated between India and China (Figure 6). The population is 26.5 million with an annual growth rate of 1.3%. The Central Bureau of Statistics reported 2010 that 25% of the population in Nepal lived below the poverty line. According to the human development index,

the country´s living standards sit below the average of south Asia [80]. Despite this, Nepal has made steady progress in health outcomes for its population. The number of births every year is approximately 720,000 and with regards to achievements in child and maternal health, Nepal was one of the countries to meet both MDG four and five ahead of schedule [2]. Child mortality actually dropped 73% from 1990 to 2014, surpassing the MDG target of two-thirds. This is partly the result of national policies and increased coverage of both maternal and child care interventions through a community based program [81]. Unfortunately, the reduction rate in neonatal mortality has not kept the same pace.

Figure 6. Map of Nepal (with permission from www.maps.com)

Although Nepal was the first low-income country to launch a national newborn strategy in 2004, neonatal mortality has only dropped at half the pace compared to child mortality. Reduction in early neonatal mortality has stagnated even more and now accounts for 85% of all neonatal deaths in Nepal [82]. Nepal reported 22.4 stillbirths per 1,000 pregnancies in 2011 and since then the reduction of stillbirth rate has been slow [3].

Rationale of the thesis

Despite available evidence-based interventions that can reduce the global burden of intrapartum stillbirth and neonatal mortality and the efforts to implement them, progress is clearly behind the trend seen for reductions of deaths in the post-neonatal period. In this thesis we study the implementation of training in neonatal resuscitation with a mixed methods approach. In a qualitative baseline context evaluation, we explore the perceptions of teamwork among delivery staff in caring for neonates in need of resuscitation. We then hypothesized that by implementing HBB together with a QIC, perinatal mortality could be reduced in a low-income facility setting studied in a prospective cohort study. Furthermore, we explored if postnatal care in such a setting is ready to handle the potential increased number of survivors in the neonatal period. Finally, using video recording observations, we attempt to answer the question whether there is some selection process in play when health workers decide which infants to resuscitate (Figure 7).

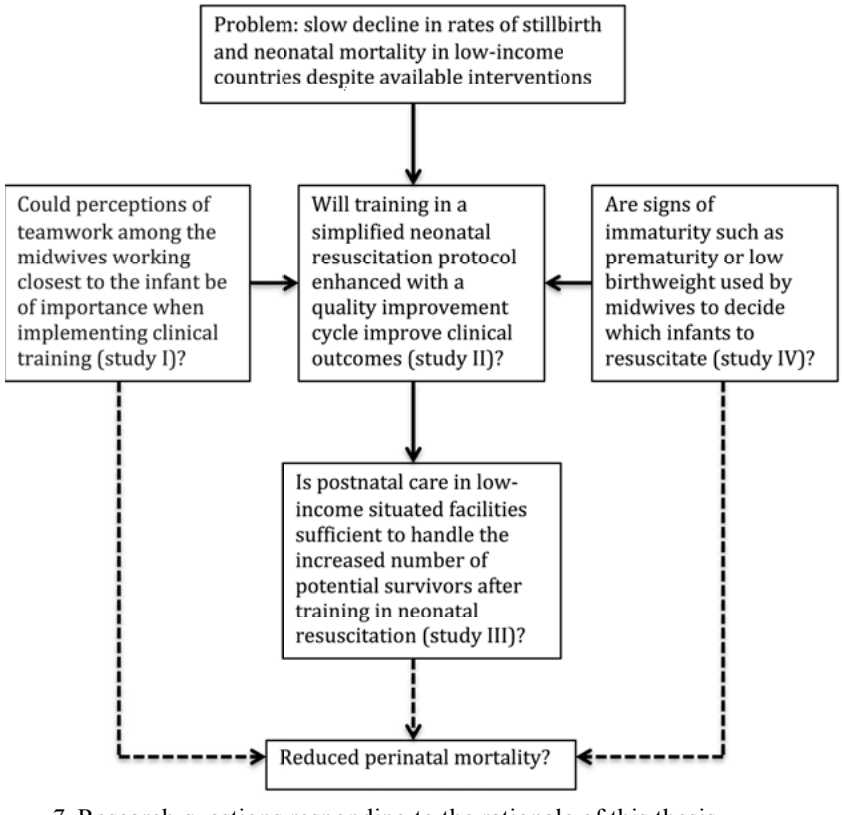

Figure 7. Research questions responding to the rationale of this thesis

Aim and objectives

The overall aim of this thesis was:

To study the implementation strategy of a simplified neonatal resuscitation protocol at a maternity hospital in a low-income setting using a mixed methods approach.

The specific objective for each paper were:

Paper I
To explore nurse midwives' perceptions of teamwork when caring for a newborn in need of resuscitation in a low-income setting

Paper II
To improve adherence to the Helping Babies Breathe neonatal resuscitation protocol and reduce perinatal mortality by using a quality improvement cycle in a tertiary hospital in Nepal

Paper III
To describe the time and cause of in-hospital neonatal deaths before and after Helping Babies Breathe training at a maternity health facility in a low-income setting

Paper IV
To compare neonatal resuscitation of low birth weight and normal birth weight infants born at a facility in a low-income setting

Methods

A co-operation between Uppsala University and Patan Academy of Health Sciences in Nepal (PAHS) was initiated, and a hospital-based study was launched in the middle of 2012. Both quantitative and qualitative methods were used. A prospective cohort study was applied for quantitative data collection with a baseline period from July to December 2012, and an intervention period from January to September 2013 [83]. During the course of the study, information on socio-demographic status, obstetric history, delivery outcome and postnatal care was collected. To achieve data on changes in clinical practice regarding neonatal resuscitation, video cameras were mounted at each newborn care station. In order to explore the perceptions of teamwork among the staff working closest to the infant during delivery, focus group discussions were performed during the baseline period.

Study setting

Paropakar Maternity and Women´s Hospital is a tertiary government hospital providing gynaecological and obstetrical services to the Kathmandu valley. It also serves as a central referral point for Nepal (Figure 8). The hospital provides antenatal, delivery and postnatal care for women and newborn infants, as well as academic programs like postgraduate diploma and Masters in obstetrics and gynecology. Approximately 22,000 deliveries take place every year and there are 425 beds. Ahead of the study, stillbirth rate was 19 per 1,000 deliveries and early neonatal mortality rate was 9 per 1,000 live births. Maternal mortality was 17 per 100,000 deliveries, and the rate of Caesarean Section was 20 % [84].

Births take place at three wards in the facility. The Maternal and Newborn Service Center is staffed by nurse-midwives and tend to low-risk vaginal deliveries. The Labor Room cares for high-risk vaginal deliveries with a human resource of nurse-midwives and obstetricians. Finally, in the case of cesarean section, delivery takes place in the Operation Theater, staffed by anesthesiologists, obstetricians and nurse-midwives. Residents, and medical and nurse students, mainly train in the Labor Room. Occasionally, delivery

took place at the Admission Room. If needed, resuscitation of newborn infants was performed at designated tables in each ward.

The hospital also features a postnatal ward staffed by nurse-midwives and a neonatal intensive care unit (NICU) consisting of 30 beds along with an attached Kangaroo Mother Care (KMC) unit of four beds. The NICU treats infants suffering of severe neonatal complications from premature birth, intrapartum-related events, neonatal infection, hyperbilirubinemia or congenital malformations. The KMC unit admits infants with low birth weight (<2,000 grams) or premature infants from 34 gestational weeks after 24 hours of observation in the NICU. Nurses and junior doctors staff the NICU with neonatologists attending in daytime.

Figure 8. Paropakar Maternity and Women´s Hospital situated in Kathmandu at the time of the study. This building was partly destroyed in the 2015 Gorkha earthquake and was later evacuated and demolished.

Delivery at the facility was free of charge and an incentive fee of 1,000 Nepali Rupies, corresponding to nine Euros, was offered at discharge to encourage facility delivery as opposed to home delivery. Apart from government facilities, Nepal also feature private hospitals. Private alternatives generally offer a higher quality of care but are inaccessible for most inhabitants.

Study design

The papers in this thesis used different designs in response to the four research questions posed (Table 2). In Paper I we summoned five focus groups and used qualitative content analysis to arrive at one theme and five categories. In paper II a prospective cohort with a nested case-referent design was

used along with video recordings to measure adherence to the neonatal resuscitation protocol and outcomes of intrapartum stillbirth and neonatal mortality within 24 hours. Paper III used the cases of neonatal deaths in the cohort to compare in-hospital neonatal survival before and after training in HBB QIC. Finally, paper IV used available video recordings during the study to compare resuscitation practices of low and normal birth weight infants. Full description of data collection and analysis is provided for each paper below.

Table 2. *Study design for paper I-IV in the thesis*

	Study design	Sample size	Exposure	Analysis	Outcome
Paper I	Focus group discussions with midwives	Five groups with 4-11 participants each	Topic guide and moderated discussion	Qualitative content analysis	Theme and categories
Paper II	Prospective cohort with nested case-referent	443 still births, 299 neonatal deaths; 25,108 deliveries	Neonatal resuscitation	Logistic regression	Intrapartum stillbirth; first day mortality
Paper III	Prospective cohort	299 neonatal deaths	Neonatal resuscitation	Comparative statistics	Neonatal survival
Paper IV	Prospective cohort	Video recordings of 2,253 resuscitations	Birth weight	Logistic regression	Resuscitation activities

Intervention

The general design of the study to evaluate an intervention of HBB QIC at Paropakar facility was performed in May 2012. The trial was registered (ISRCTN97846009) and a study protocol was published later the same year [83]. Meetings were held with the administration of the hospital, the Midwife Society of Nepal, the Ministry of Health in Nepal, the collaborators at Patan Academy of Health Sciences and funders to facilitate the study and create participation. Tools for data collection were produced and an on-site research team consisting of one research coordinator and several surveillance officers were recruited. The baseline portion of the study started in July 2012.

Quality Improvement Cycle

In November 2012, two months ahead of the intervention, the study team organized a workshop together with hospital leadership, nursing supervisors and the in-charges of each ward. Those participants formed a quality im-

provement team (QIT) and discussed the barriers to improved skills in neonatal resuscitation practices at the hospital. With support from an interim analysis of the baseline data, quality improvements were suggested based on available literature and resources within the facility [53, 85]. The QIT decided to set a goal of reducing intrapartum-related deaths by 50%. Meetings with all staff of each delivery unit were conducted and causes of low adherence to resuscitation guidelines from the point of view of the staff were identified. It was found that better clinical skills through training, equipment support, intermittent reviews and meetings for reflection of the practices were in demand. After meetings with all delivery wards, the QIT decided on a multi-faceted intervention of universal HBB training and refresher training together with five quality improvement components (Table 3). All staff participated in the different components of the quality cycle, which were facilitated by the in-charge at each unit. HBB trainers facilitated the HBB training and refresher training.

Table 3. *Components of the Helping babies Breathe (HBB) Quality Improvement Cycle (QIC) implemented at a maternity facility in Nepal*

Component	Activity	Facilitator
HBB training	Two-day training; first day on HBB package and second day on components of QIC	HBB trainers
Weekly review	Weekly review and reflection meetings on the progress of HBB QIC standards	Unit in-charge
Daily skill check	Each staff member completes a bag-and-mask skill check before starting duty	Unit in-charge
Preparation before birth	Preparation before each birth according to HBB protocol	Unit in-charge
Self-evaluation	Using the checklist in the HBB package, staff complete a self-evaluation after each delivery	Unit in-charge
Peer-review	Peer-review after each resuscitation using the HBB protocol poster at the resuscitation table	Unit in-charge
HBB refresher training	One-day refresher training after six months	HBB trainers

Implementation

The intervention started in January 2013 with a two-day training in HBB and QIC for staff working at the three delivery units. All staffs, including medical doctors, nurses and students were invited to attend the sessions. After training, the equipment and tools in the HBB package were provided to the units. Mannequins for daily skill checks were placed at the entry of each unit. Posters were applied to the wall at the resuscitation tables and self-evaluation checklists were provided. A total of 12 weekly review meetings were scheduled in each unit. To follow the progress and visualize the HBB

QIC concept for all staff, progress boards were displayed at the units and used during the weekly meetings (Table 4).

Table 4. *Progress boards for Helping babies Breathe Quality Improvement Cycle placed at each ward within the facility*

	Week 1	Week 2	Week 3	Week…
Macerated still birth				
Fresh still birth				
Neonatal death				
Non-breathing baby				
Non-breathing baby ventilated				
Ventilation within one minute				
Resuscitation corner available				
Adequate function of suction				
Adequate function of bag-and-mask				
Mannequin for skill check				
Weekly review meeting				

Sample size

In order to detect a change in perinatal mortality from the intervention a conservative power calculation was performed. With a baseline perinatal mortality of 30 per 1,000 deliveries, the delivery rate at the hospital (22,000 per year) indicated that a 20% reduction in mortality rate would be detectable within a six-month time frame (alpha 0.05, beta 0.20).

Data collection and analysis

Paper I

To address the research question of teamwork perceptions, focus group discussions was chosen as the method of data collection for paper I. In order to retrieve varied data on thoughts, actions and communication within the group, this was found to be preferred to, for example, in-depth interviews [86]. Five focus groups from different wards were recruited by purposive sampling with the aim to have 6-8 people in each group [87]. Staff available for sampling was however limited as most of the staff were busy with clinical duties. Supervisors from the wards formed their own group (Table 5).

Focus group discussions were performed during the baseline of the study in October 2012. Discussions were moderated by a Nepali midwife with experience from qualitative studies and from the context. Data were transcribed into Nepali and then translated by a professional translator. A topic guide

was used and the authors developed it collectively. It was tested in a short pilot with midwives provided by the Midwife Society of Nepal who had experience from similar facilities in Kathmandu. The topic guide contained questions on teamwork collaboration in situations with infants undergoing neonatal resuscitation and related perceptions of hierarchies, routines and possible obstacles to effective clinical practice.

Table 5. *Characteristics of the five focus groups sampled for discussion on teamwork perceptions at a maternity hospital in Nepal*

Group	Participants	Years of experience
Labour room	4 female	3-24
Operating theatre	5 female, 3 male	6-32
Supervisors	11 female	20-33
Maternal and newborn service centre	4 female	4-13
Admission room	6 female	1-6

The final text was analyzed with qualitative content analysis using software OpenCode (Freeware, Umeå University) [88]. Meaning bearing units were condensed and coded. After going through the text several times, the codes were sorted into sub-categories. Using abstraction and assigning the subcategories to categories, a back and forth process was performed by two of the authors together (Table 6).

Table 6. *Example of the coding and categorizing process while analyzing material from focus group discussions with nurse midwives in Kathmandu, Nepal*

Text	Code	Subcategory	Category
It is our duty as staff to ensure the safety of mother and child	Team ensures patient safety	Knowledge in the team	Benefits and challenges of working together
In my case the authorities openly said that the death was my responsibility	Blamed for baby's death	Coping with negative outcomes	Dealing with systemic and personal mistakes

From the categories, we went back to the original text to find representable quotes to describe each category. The findings were presented to all authors and one theme running through all the categories was finally decided upon.

Paper II

A prospective cohort study with a case-referent design was applied. A surveillance system was set up in the hospital for data collection. Guided by a research coordinator, a total of 12 surveillance officers with public health background were recruited. A rotational 24-hour shift was constructed so that surveillance officers were present twenty-four hours in the admission

room throughout the study period. All deliveries at or after 22 gestational weeks were included in the study. As the total number of deliveries was too large to include in the study, 20 % were randomly selected as nested referents using randomization. The process used an opaque jar at admission filled with 20 yellow and 80 white balls. When a woman was admitted for delivery a ball was drawn. When a yellow ball was selected, the woman was included in the referent population if consent was given. When all balls were drawn, the research group would start over with all 100 balls in the jar. A referent form was attached to the hospital chart that would follow the woman until discharge. In the case of stillbirth or neonatal death, a case form was attached. If a referent mother delivered a stillbirth or if her infant died within the hospital during the neonatal period, transfer to the case population was performed. Data collection forms (A, B, C and D), were designed and deployed in the study. The design of them followed collaboration between the research team and the pediatricians and obstetricians at the facility (Table 7).

Table 7. *Forms for data collection during the prospective cohort study in Nepal*

Data collection form	Target population	Description
A: Referent form	Referents	Demographic information, obstetric history, intrapartum monitoring and neonatal information
B: Case form	Cases of stillbirth and neonatal deaths	Demographic information, obstetric history, intrapartum monitoring, neonatal information, and outcomes of stillbirth and neonatal death
C: interview form	Referents and cases	Socio-economic characteristics
D: Video observation form	Referents and cases[1]	Place, date, time, gestational age, Apgar scores, birth weight, resuscitation practices and sex of all resuscitated infants captured on video

1 During the first four months of baseline all video recordings of resuscitation were analysed

The surveillance officers collected data from the referent (form A) and case (form B) population on demographic information, previous obstetric history, intrapartum monitoring and outcome (Table 8). All referents and cases were also interviewed (form C) using a standard form from Nepalese health care authorities. Motion-triggered charge-coupled device (CCD) cameras (model MTC-505DH) were installed over the resuscitation tables located at the different wards where delivery took place. The obtained videos contained time stamps to allow for coupling with the hospital register of the recorded delivery. The video was analysed by the surveillance team trained in utilising a data collection tool (form D) in order to retrieve data for initiation of resuscitation measures of stimulation, suction, ventilation and provision of oxygen. It was also noted if the infant was crying or not after birth. Non-crying was considered a failure to initiate breathing and thus used as a proxy for the clinical indication of neonatal resuscitation initiation.

Table 8. *Definitions of primary outcomes in the Helping Babies Breathe study*

Variable	Definition
Perinatal mortality	Death during the perinatal period; including stillbirth of a viable fetus after 22 weeks of gestation or birth weight >500 grams and neonatal deaths within the first 7 days of life
Stillbirth	Birth of a viable fetus after 22 weeks of gestation or birth weight > 500 grams, with Apgar score of 0 at 1 and 5 minutes
Antepartum stillbirth	Birth of a viable fetus after 22 weeks of gestation or birth weight > 500 grams, with Apgar score of 0 at 1 and 5 minutes, with signs of maceration or no fetal heart rate at admission or at the onset of labour
Intrapartum stillbirth	Birth of a viable fetus after 22 weeks of gestation or birth weight > 500 grams, with Apgar score of 0 at 1 and 5 minutes, with no signs of maceration or where fetal heart rate was detected at admission or at the onset of labour
First-day mortality	Death of a live-born infant within 24 hours of life

Statistical analysis was performed using Statistical Package for the Social Sciences (IBM, New York). Pearson´s Chi-square test, t-test and Wilcoxon rank-sum test was used to compare mortality-related outcomes and background characteristics of the referent population in the baseline and intervention period. Multiple regressions were performed in order to establish any change in perinatal outcome. The model was adjusted for the background characteristics that were different in the referent population during baseline and intervention. Univariate regression was conducted of the video data to determine any change in clinical practice after the implementation of HBB QIC. Statistical significance was set at *p*-values below 0.05.

Paper III

This paper used data from the prospective cohort study on birth weight, gestational age, mother's age and neonatal outcome. The causes of neonatal deaths and the timing of them (day 0-27) were retrieved from hospital registers. Only in-hospital deaths were used. Senior neonatologists working in the NICU determined the cause of death (Table 9).

Table 9. *Causes of neonatal deaths used by neonatologists at the facility*

Cause of death	Definition	Description
Congenital anomaly	Clinical suspicion	Many cases, such as cardiac malformation, passed before cause was established as diagnostics, e.g. cardiac sonograph, was not available
Preterm birth	Gestational age < 32 weeks	Last menstrual period was used to determine gestational age
Intrapartum-related	Neonatal encephalopathy	If criteria for neonatal encephalopathy was not fulfilled, infants with an Apgar score below 4 at 5 minutes were also included in this group
Neonatal infection	Clinical suspicion and pathological lab tests	Example given: sepsis, meningitis and pneumonia
Other causes	All other causes	Example given: renal failure, kernicterus, and necrotizing enterocolitis

Data were analyzed with Stata 13.1 (Stata Corp, College Station, TX, USA). Pearson´s chi-square test was used to compare outcome measures and the causes of neonatal death in the baseline and intervention period. Kaplan-Meier survival estimates were performed to describe and compare the timing of all neonatal deaths and also for each cause of death. To determine if survival estimates were different in the two study periods, log-rank tests were applied. Statistical significance was set at *p*-values below 0.05.

Paper IV

Data collected from observations of the video recordings were used together with information on birth weight, gestational age, sex and Apgar scores at one and five minutes. Out of 257 recordings of resuscitations performed during October and November 2012, 50 were randomly selected to assess inter- and intra-reliability of the observations. The reliability was found to be high for use of bag-and-mask and suctioning, but lower for oxygen administration and stimulation [78]. The reliability of whether the baby was crying or not was low (56%), but this was assumed to be uncorrelated to birth weight. We also compared the data on crying versus non-crying with cut-offs for Apgar scores at one minute and five minutes.

After starting the study, the workload for the surveillance officers was found to be unmanageable with regards to the number of videos for observation. During the first part of baseline *all* resuscitations captured by the video cameras were analyzed but this procedure was abandoned from November 2012. To achieve better power than in Paper II, when only case and referent observations were used for both study periods, we included more observations from baseline in this paper. Thus, the data that represents baseline in Paper

IV was restricted from July 2012 to October 2012 including all resuscitations. From November 2012, and trough the intervention period only cases and referents captured on video were analyzed.

LBW was defined according to the WHO definition of a birth weight less than 2,500 grams [89]. When reviewing data regarding birth weight, we found a problem of over-registration of birth weights at multiples of 250 grams. This is a known source of error in data of birth weight, especially from low-income settings, called heaping and it was adjusted for at the cut off for LBW at 2,500 grams [90]. Pearson´s chi-square test was applied to compare resuscitation practices for LBW and normal birth weight (NBW) infants during baseline and intervention. Logistic regression was then used to identify any difference in odds of receiving the four interventions during resuscitation of LBW and NBW. We adjusted for the place of table within the facility and the sex of the infant. Baseline and intervention period were analyzed separately and subsequently as one dataset adjusting for the intervention of HBB QIC. Statistical significance was set at *p*-values below 0.05.

Data management

A full-time data entry manager was responsible for quantitative data management. All forms were re-checked for discrepancies before entering the data in a CSPro database (The Census and Survey Processing System), a public domain software package developed and supported by the U.S. Census Bureau. The research coordinator verified at least 10 % of the forms for accuracy from its primary source. In order to avoid data loss a protocol for data tracking was developed. Similarly, bi-monthly internal and external verifications or audits were conducted to ensure data completeness and accuracy. An independent data monitoring committee, which was formed before the study started in June 2012, performed quarterly reviews of interim data for completeness, quality, and adherence to ethical requirements. If any form was incomplete ahead of entry into CSPro, the research coordinator went back to the primary source to minimize missing data. This was performed to the greatest extent possible. However, some background information on mothers was not possible to retrieve and in those cases, multiple imputation was performed [91].

Ethical considerations

Approval for the study was received from Nepal Health Research Council (Reg. No. 37/2012) and the Ethical Review Board of Uppsala University (dnr 2012/267). The hospital management supported and endorsed the study.

Quantitative data

All women selected as referents at admission and all women that had a still-birth or gave birth to an infant that died within the hospital signed a written consent. In case of illiteracy, the consent form was read to them. Participants could withdraw from the study at any time of their choice. Regarding video recordings, only the infants and the hands of health care providers were in the field of vision to ensure confidentiality of the staff. No sound was recorded. Hard copies of video recordings, data files and forms were kept in a locked filing system in a secure room.

Qualitative data

All participants signed a written consent ensuring confidentiality ahead of the focus group discussions. Quotes were de-identified already during data collection. Members were not coerced into participation and withdrawal was possible at any point. The moderator kept notes and recordings in a safe and locked place at all times, except for a short period of time when the data was used by the translator after which is was returned to the moderator.

Results

The exploration of teamwork perceptions during baseline (Paper I) found a theme where nurse midwives look for a universal display of resuscitation protocols, shared medical responsibilities and management involvement when dealing with clinical incidents. The HBB QIC intervention (Paper II) demonstrated a reduction of intrapartum stillbirth and neonatal mortality within 24 hours, as well as increased adherence to the clinical protocol. Neonatal deaths related to intrapartum complications were reduced and premature infants survived additional days in the neonatal period after the HBB QIC implementation (Paper III). Low birth weight does not seem to be a predictor for deferred neonatal resuscitation in the studied context (Paper IV). Below these findings are further elaborated upon.

Perceptions of teamwork

From the analysis of focus group discussions (Paper I) we found one theme running through all the five categories (Table 10):

Table 10. *Categories and theme from focus groups discussions with nurse midwives at a maternity hospital in Kathmandu, Nepal*

Categories	**Theme**
Benefits and challenges of working together	Looking for comprehensive guidelines and shared responsibilities in neonatal resuscitation to avoid personal blame and learn from mistakes
Dealing with systemic and personal mistakes	
Importance of a strong and transparent leadership	
Protocols to cope with resuscitation	
The unpredictable working environment	

Discussions revealed a desire to have universal guidelines within the facility in order to share responsibilities and work in the same direction during neonatal resuscitation. Skills of neonatal resuscitation are relied upon, but staff described a hesitancy to use them in situations where the outcome might be unfavorable. This hesitation is partly the result of an experienced practice of hospital leadership to assign blame to person rather than to the organization in the case of clinical incidents.

The lack of a formal and universal protocol for neonatal resuscitation was highlighted during the discussions. Many of the nurse midwives had completed Skilled Birth Attendant (SBA) training before and applied those skills but there were perceptions of unclear official guidelines within the facility. Staff from Operation theatre and Admission Room explained:

> No, there is no such thing [as a protocol]. If we have to, we all carry out each other's duty

> The major problem in our hospital is the lack of proper rules and regulations ... so many changes are made in the original guidelines but they are not implemented in the hospital

The unclear responsibility and mandate of each member in the team created confusion when dealing with difficult cases of neonatal resuscitation. This sometimes made nurse midwives hesitant to begin interventions such as ventilation until more experienced or higher ranked staff arrived. The group of supervisors and staff from Labor Room noted:

> You see, when an incident takes place the doctors have an excuse, the sisters [nurses] didn´t call on time

> When it comes to addressing a [resuscitation] case everybody backs out … everyone tries to escape their responsibility … they try to shove it off to one another

The tendency of management to assign responsibility of adverse outcomes to individuals rather than to the organization caused tension and anxiety among staff. When clinical incidents were investigated, many felt it was important to stay out of the limelight to avoid personal blame and liability. In some of the wards this culture initiated spontaneous audit within the teams to prepare for questioning. Participants from Labor Room and Maternal and Newborn Service Centre described:

> In my case the authorities openly said that the death was my responsibility. I was the only one held liable

> If we don't learn lessons from the mistakes of others we might be the next ones standing for questioning

Participants often returned to the hectic working environment present in the facility. In such situations they have no time to document details in the registers, as they need to prioritize the care of mothers and infants. This was described as putting extra pressure on them as incidents tend to happen more often during work-overload.

Intervention effect on perinatal mortality

During the prospective study period a total of 25,108 deliveries took place and 4,531 of them were enrolled as referents. A total of 299 neonatal deaths and 443 stillbirths were registered (Figure 9).

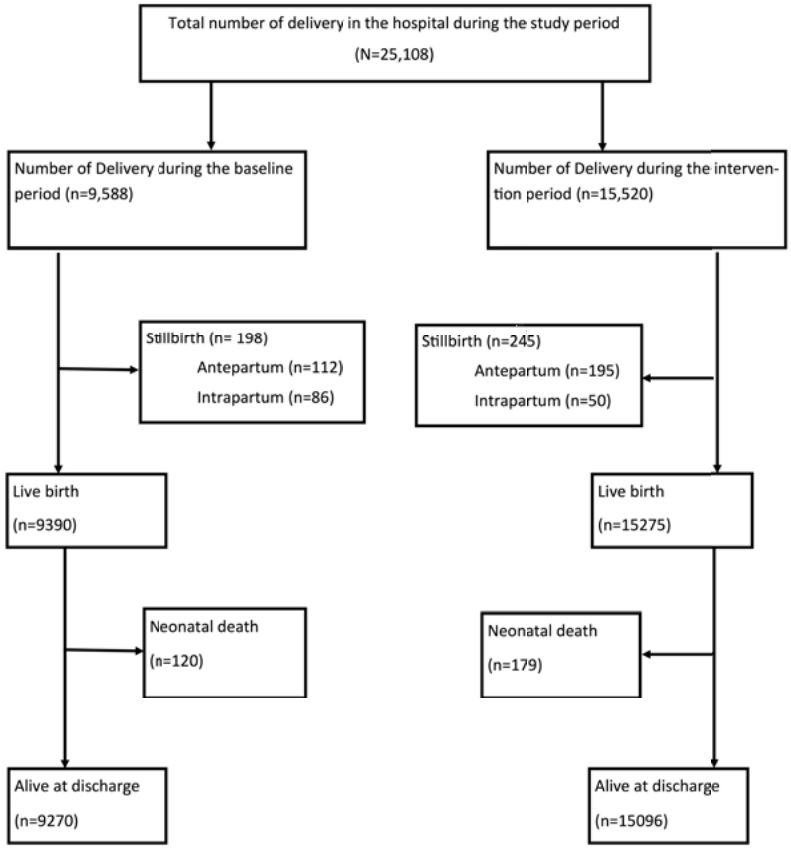

Figure 9. Flowchart of the baseline and intervention populations

The rate of perinatal mortality was lower ($p<0.01$) in the intervention period (23.0/1,000 deliveries) compared to the baseline period (30.9/1,000 deliveries); the intrapartum stillbirth rate was lower ($p<0.01$) in the intervention period (3.2/1,000 deliveries) compared to baseline period (9.0/1,000 deliveries); and neonatal mortality within 24 hours was lower ($p<0.01$) in the intervention period (1.9/1,000 live births) compared to baseline (5.2/1,000 live births). Rate of antepartum stillbirth was unchanged (Paper II).

The background characteristics of the referent population were different between the two study periods regarding the number of antenatal check-ups

(ANC) the mothers performed (4 or more versus less than 4) and the gestational age of the infants. A larger proportion of the mothers attended the minimum four visits of ANC in the intervention period (33.8% versus 30.0%) and there were a larger proportion of term infants (at or >37 weeks of gestation) in the intervention period (91.1% versus 90.3%). Thus, we adjusted for those two factors in the multiple regression analysis when calculating odds for the primary outcomes after HBB QIC implementation in the case-referent population (Table 11).

Table 11. *Odds for mortality outcomes after Helping Babies Breathe Quality Improvement Cycle intervention*

Outcome	Adjusted Odds ratio[a]	95% CI lower	95% CI upper
Perinatal mortality	1.03	0.84	1.25
Stillbirth	1.04	0.84	1.30
Intrapartum stillbirth	**0.46**	0.32	0.66
First-day mortality	**0.51**	0.31	0.83

[a] Multivariate regression analysis demonstrating odds for mortality outcome adjusted for full antenatal attendance and gestational age (preterm or term)

The odds for intrapartum stillbirth and first-day mortality were lower after the intervention, corresponding to reductions of 54% and 49%, respectively. There was, however, no change in the recorded perinatal mortality or overall stillbirth after adjusting for confounders (Paper II).

Intervention effect on adherence to protocol

During the study of HBB QIC, resuscitations of infants captured by the motion-triggered video cameras were analyzed. A total of 488 and 588 resuscitations were registered in the baseline and intervention period, respectively. Odds for suctioning were lower (OR 0.13 95% CI 0.09-0.17) and odds for ventilation were higher (OR 2.56 95% CI 1.67-3.93) after the intervention (Table 12).

We also used information on non-breathing infants to investigate the clinical indication for correct initiation of ventilation. In the baseline period, none of the non-breathing infants (0/31) in the referent population received ventilation within 60 seconds, whereas after the intervention, 84% (73/87) of the infants in need of resuscitation received ventilation within the time period stipulated in the protocol.

Table 12. *Resuscitation of referent infants before and after Helping Babies Breathe Quality Improvement Cycle*

	Baseline[a] n (%)	Interv[b] n (%)	OR[c]	95% CI lower	95% CI upper
Stimulation					
No	255 (52.3)	437 (74.3)	Ref		
Yes	233 (47.7)	151 (25.7)	0.38	0.29	0.49
Suctioning					
No	66 (13.5)	324 (55.1)	Ref		
Yes	422 (86.5)	264 (44.9)	0.13	0.09	0.17
Ventilation					
No	457 (93.6)	501 (85.2)	Ref		
Yes	31 (6.4)	87 (14.8)	2.56	1.67	3.93

[a] The referent population in the baseline that received resuscitation captured by video
[b] The referent population in the intervention that received resuscitation captured by video
[c] Odds ratios for stimulation, suctioning or ventilation (bag-and-mask within 60 seconds)

Causes of neonatal deaths

Out of 24,665 live births during the whole study period, 299 died in the neonatal period, of them 120 in the baseline and 179 in the intervention period. As demonstrated previously (Paper II), rate of mortality within 24 hours was reduced after the intervention. However, overall, early and late neonatal mortality was unchanged. Neonatal death from intrapartum-related complications was reduced from 51% to 33%, but deaths from all other causes during the neonatal period were unchanged (Paper III). Introducing the day of death into the analysis, Kaplan-Meier survival analysis indicated that the time of death in the neonatal period was postponed ($p<0.01$). The contribution to this postponement was provided by deaths from complications of intrapartum-related events and preterm birth whereas the timing of neonatal deaths from congenital anomalies, neonatal infections and other causes was not changed by the intervention (Figure 10).

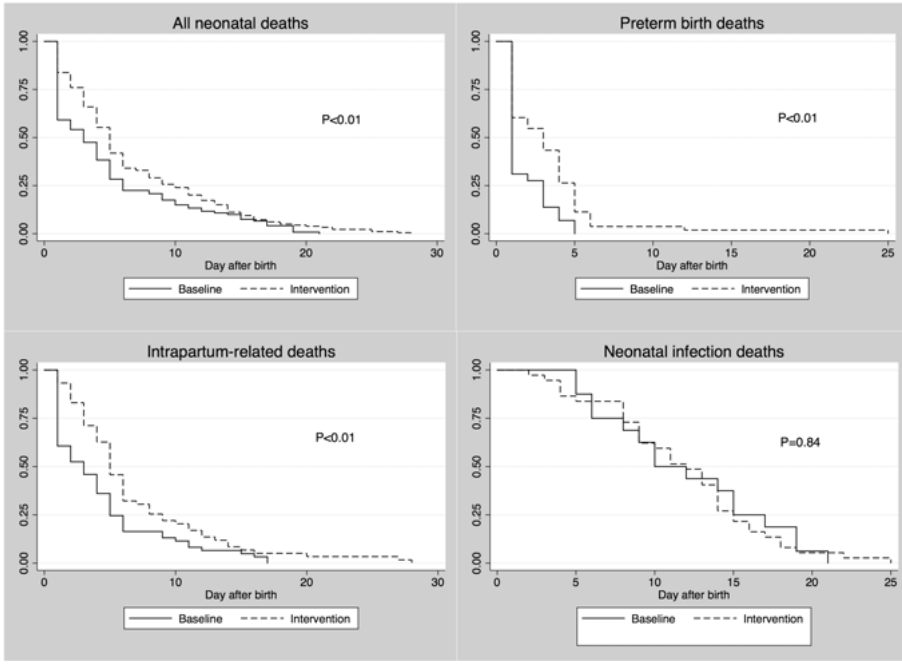

Figure 10. Kaplan-Meier survival estimates for neonatal deaths, deaths from complications of preterm birth, intrapartum-related conditions and neonatal infection at baseline and after intervention period during the Helping Babies Breathe trial at a maternity facility in Kathmandu, Nepal (*p*-values calculated using log-rank test)

Resuscitation practices

During the first four months of the baseline and trough the intervention period, a total of 2,253 resuscitations recorded on video were included. Of the non-crying infants, assumed to be in need of resuscitation, 250 were LBW and 941 NBW infants (Figure 11). Non-breathing infants in both weight groups were more frequently ventilated after the intervention of HBB QIC (p<0.01) whereas all other practices of stimulation, suction and provision of oxygen was more common in the baseline than in the intervention period (p<0.05). For the whole study period, odds of suctioning of LBW infants were lower (aOR 0.53 95% CI 0.34-0.82), and they were higher for ventilation (aOR 1.73 95% CI 1.24-2.42). There was no difference in odds for stimulation and provision of oxygen. Adjustments were made for the HBB QIC intervention, gender of the infant and place of delivery in the multivariate regression model (Paper IV).

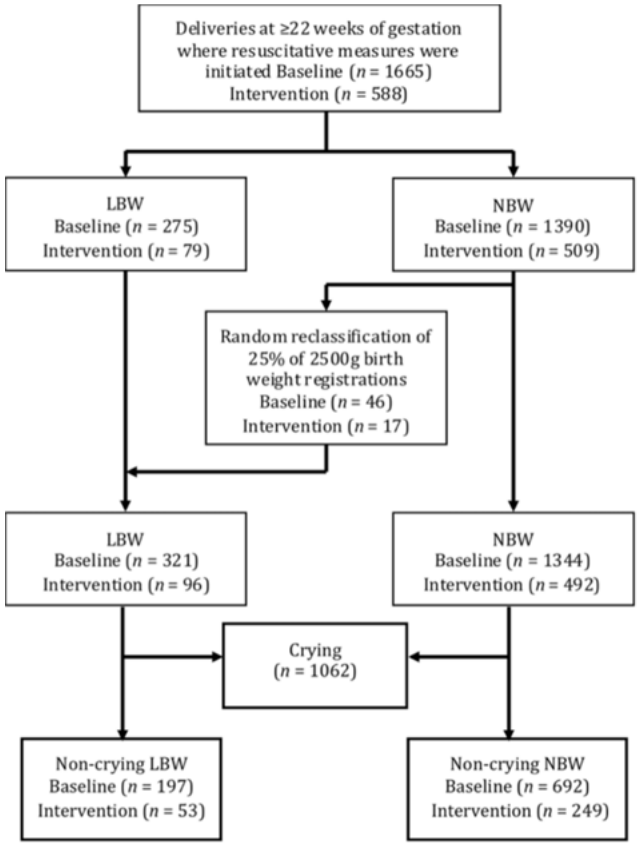

Figure 11. The total number of low birth weight and normal birth weight infants where resuscitation was recorded included in Paper IV from the Helping Babies Breathe study in Kathmandu, Nepal

Discussion

Interpretation of results

Health care improvements required to reduce the burden of intrapartum related mortality are mainly straightforward. Neonatal resuscitation and other simple interventions could prevent many cases of neonatal death when implemented under ideal conditions. However, ideal conditions will not prevail in any setting. Also in high-income countries simple steps in an evidence-based protocol for neonatal resuscitation are not always followed [54]. Therefore, evaluating the context of the target setting and bridging the know-do gap when intervening for improved neonatal survival has come into focus. In this area qualitative research such as our study comes into an important play [62]. Providing health care is a complex combination of people and knowledge were organizational issues, previous experiences of the providers, cultural factors and the specific situation interact to create the final result.

Midwives in our study asked for universal display of guidelines so that all staff can work in the same direction. Previous studies on simple dissemination of written guidelines to staff has demonstrated it is usually ineffective when it comes to changes in practice, although it might leave supervisors with a reassuring comfort that routines are in place [67]. Furthermore, when comparing groups of anaesthesiologists in Canada where one of the groups used the neonatal resuscitation protocol chart in the emergency room and the other group did not, there was no difference in retention of skills [92]. However, when baseline resuscitation skills are low, displaying charts of the protocol could provide support for feedback to the group after cases of resuscitation [93]. Also, with a chart as reference, peer review after a resuscitation case is clear and simple. Although not yet published, data from our study in Nepal demonstrates that peer review could play a part in retaining skills in neonatal resuscitation following HBB training [83]. Displaying the protocol for neonatal resuscitation will also make the implemented guideline universal and clear for everybody involved. This is an example of the complex interaction between staff working in health care, and the study in Malawi also revealed that unclear protocols could be a barrier for initiation of neonatal resuscitation [73].

The findings in Paper I also indicated that staff looks for a structured way to deal with incidents and that management needs to be involved in that process. Personal mistakes are only one little part of medical incidents and organizations should take the opportunity to learn from adverse outcomes to better prevent them in the future [94]. It has been hard to prove any improvement of mortality and morbidity from clinical audit in high-income settings, but the feedback of such audit to staff can improve health worker performance [95]. As our study also suggests that such audit could relieve the staff from anxiety around personal performance in difficult resuscitation cases it should be considered in this setting. Clinical audit will also enable management to track changes of practice in the organization [96]. Criterion-based clinical audit seems to be feasible in low-income settings but it needs to be further investigated how such a system should be designed and implemented [97].

Our study added to the growing evidence base of HBB implementation in low-income settings. Similar to our Nepal-based study, previous studies in Tanzania and India, demonstrated a reduction of intrapartum stillbirth and reduced or unchanged early neonatal mortality [45, 46]. This supports the validity of outcome findings, and that HBB training has the potential to reduce mortality in such settings. These are important findings but the question of sustainability is also important and still relevant, emphasized by the HBB feasibility study in Rwanda [56]. Some other previous initiatives of team training in neonatal resuscitation also initially reduced neonatal mortality but changes were not sustainable [98, 99]. We have tried to address this problem of sustainability by using the QIC in Nepal. This strategy is supported by a Cochrane report on effectiveness of implementation strategies in healthcare which reported that educational meetings together with interactive sessions have the potential to change behaviour in complex clinical situations [68]. Although we cannot unbundle the package of QIC to detect what parts that caused the effect of outcome measures, it seems to be a feasible method of implementation. In a forthcoming publication we explore the retention of skills with bag-and-mask ventilation six months after HBB QIC [100]. Findings suggest that the retention of skills was mostly associated with daily bag-and-mask skill checks and the use of a self-evaluation checklist after every delivery. A routine preparation before each birth and weekly review meetings were less associated, and peer-review after resuscitation cases was not associated with skill retention. Each component of the QIC needs to be further tested and evaluated, preferably also in district and community settings, but parts of the package clearly seems to be a favorable add-on to HBB training.

Intrapartum stillbirth and mortality in the first 24 hours of life were reduced, but perinatal mortality was unchanged after adjustment for confounders in our study as presented in Paper II. The confounders we found to be different in the two study periods were a higher incidence of premature infants in the baseline period and a better ANC attendance in the intervention period. As the combination of these two confounders favors the intervention period, they exercise a plausible effect on our outcome measure of perinatal mortality.

Furthermore, in Paper III we demonstrated that mortality during the whole neonatal period was unchanged by the intervention although death from intrapartum-related complications was reduced and preterm infants survived additional days. One can argue that vulnerability among the survivors could have been higher after the intervention as the prevalence of low Apgar scores was higher among those survivors. These findings suggest that postnatal care was not sufficient to maintain gains in survival on the day of delivery [101, 102]. Thus, although training in neonatal resuscitation can improve neonatal outcomes in low-income settings, the quality of care post resuscitation also needs to be addressed. Currently, a large study of HBB implemented together with Essential Newborn Care, as suggested by a WHO program, is underway in 71 facilities in India and Kenya [103]. The Essential Newborn Care program teaches evidence-based management of the newborn infant from the moment of birth through the first days of life until discharge. A similar package building on the HBB educational concept is Helping Babies Survive (HBS) [104]. HBS aims to prevent neonatal death from severe infection and complications of prematurity by teaching management of danger signs in the newborn infant; prevention of hypothermia; promotion of early breast-feeding; of KMC for low birth weight infants; and alternative feeding strategies when nutrition is poor. HBS is evaluated as a feasible and acceptable educational package, but its effect on neonatal mortality has not been tested to date and no on-going trials are to our knowledge registered [105].

Our study also, for the first time, presented data verifying a change in actual clinical practice after training in HBB. The rate of ventilation captured by the video cameras was significantly higher while the rate of suctioning was lower after the intervention. Stimulation was also less frequent after the intervention, possibly reflecting an increased awareness of apneic infants as health workers moved quicker to ventilation when drying and was not sufficient to initiate breathing. Ventilation within the golden minute for referent infants registered as non-crying increased from none (0/31) in baseline to a majority (73/87) after the intervention, clearly indicating a robust change in practice [106]. The use of suctioning was thus reduced, but the prevalence was still high (45%) after the intervention. This presents a challenge as in-

ternational guidelines from 2015 state that routine suctioning should not be performed on any indications, not even non-breathing infants born through meconium stained fluids as was the previous recommendation [39]. But the practice of suctioning of the airways is more complex and multi-faceted. The international recommendation refers to deep suctioning of the lower airways, while the HBB protocol recommends to use a bulb syringe suction device only 5 cm beyond the lips to clear the airway if breathing is not established after drying and stimulation [42]. This is in line with international guidelines if ventilation is indicated. The still high usage of suctioning of the lower airways also after the intervention in our study suggest the indication for suctioning, and how it is performed, needs to be emphasized further in the HBB protocol.

We also used the results from video recordings to explore if there was any selection of infants where health workers chose not to resuscitate. We could not find any support for the hypothesis that resuscitation of low birth weight infants was deferred [26]. On the contrary, odds for ventilation were higher for the group of non-breathing low birth weight observed in the study. Odds for suctioning of low birth weight infants were lower, but suctioning was excessively used, and ventilation is the most crucial step to initiate in a non-breathing infant [44]. One major weakness in our study was that we had no information of decisions taken outside the resuscitation tables. Health workers could have decided not to bring an apparent stillbirth or apneic live birth to the resuscitation table, especially if premature or of very low birth weight.

When implementing large scale training in neonatal resuscitation in low-income settings ethical considerations arise. As quality of neonatal care is improved, indeed we expect mortality and morbidity from intrapartum-related complications to be reduced [28]. However, the risk of morbidity among resuscitated survivors, especially preterm infants, must also be considered [107]. Over the last decades, the quality of care for extremely and very preterm infants has driven the development of neonatal care in high-income settings [108]. Over time, improvements have resulted in an increased number of early survivors with unchanged morbidity [109]. Similar to what our findings suggest, investments in postnatal care has been required also in high-income settings to subsequently reduce overall mortality [110]. Increased investment in NICU resources, especially in middle-income countries, is underway. As the quality of recently added neonatal intensive care is a problem, morbidity from neonatal complications is highest in that group of countries [25, 111]. However, extremely premature infants rarely survive in low-income contexts, especially in community settings, highlighting the rationale to continue the investment in basic neonatal interventions [23]. Most births are term infants, and approximately 85% of all preterm infants are moderately preterm (born at or after 32 weeks of gestation). As morbidi-

ty in this group of infants is considerably lower, basic interventions for increased neonatal survival should not be deferred because of the long-term risk of neurodevelopment impairment [112].

Few studies have systematically addressed the still lingering question of long-term outcomes of mortality and morbidity after training in neonatal resuscitation in low-income settings [28]. A promising tool to explore in future studies is the strong correlation between neurological symptoms after birth and long-term outcome. The incidence of neonatal encephalopathy among infants who suffered and survived an intrapartum complication has been proven to be a strong predictor of long-term neurological impairment [25]. Assessing neonatal encephalopathy in its simplified and modified form is rather straightforward and possible to apply also in low-income settings [113, 114]. Future large-scale interventions of training in neonatal resuscitation should therefore consider the inclusion of neonatal encephalopathy outcomes to explore neurodevelopment impairment following increased coverage of this life-saving intervention.

Methodological considerations

Qualitative methods

In pursuing knowledge of the complex interactions between people and their perception of the situation when caring for infants we also introduce our own views and expectations. Thus, the result will always include some level of abstraction performed by the authors to interpret the latent content of the data [115]. By observing some of the measures outlined below we tried to enhance the trustworthiness of the findings.

Credibility refers to whether the findings are believable from the perspective of the participants and it corresponds to the idea of internal validity in quantitative research. In our study the topics used in the discussions were open-ended to make way for different and contrasting views from the respondents. If participants hesitated to engage in the discussions, the moderator would encourage them. Focus groups continued until all the topics in the guide were debated and after all participants were able to respond, suggesting a saturation of the data [116]. The potential problem with gatekeepers was reduced by allowing supervisors to form a separate group [117]. The text transcribed from the discussions was varied and circled among many topics where all participants had the chance to express their views. All views from the interviewees were treated as important and were not enhanced by the frequency by which they appeared [118].

Transferability relates to the idea of external validity in quantitative research and the degree of how the findings can be generalized to other or similar contexts. When we designed the study we knew there were previous studies highlighting the need for focus on teamwork as an important factor in the care for infants. It was explored before, but mainly in high-income settings [71]. It is reasonable to expect that staff working for the infant's best outcome would recognize the teamwork of colleagues regardless where on the globe they operate. To accomplish this transferability we tried to describe the context and methods as thoroughly as possible [86]. An example of the transferability in our study was findings of self-confidence among the staff in their resuscitation skills combined with an intermittent hesitation to use those skills. This was similar to the study in Malawi where staff also sometimes experienced barriers to start neonatal resuscitation [73].

Dependability deals with if the methods used would generate a similar result if repeated. It relates to the concept of reliability in quantitative research. In qualitative research we can never measure the same thing twice as the context always will be different the second time around. But we can describe the context in detail and address any changes in it during the study. We sampled five focus groups and there were 4-11 participants in each. Ideally, there would have been 6-8 in each group [87]. The process of using the wards to form each group was defined as a purposive sampling but the availability of nurse midwives off duty created a limitation in staff available for sampling [119]. The amount of data collected was estimated to be a large enough unit for analysis when we closed data collection [120]. All focus groups were conducted in a single week and the topic guide was the same in all groups. We used the same moderator for all discussions. This is advisable, as it potentially will make comparisons more consistent [121].

Finally, confirmability describes how other researchers can find similar results with the same material. The corresponding quantitative concept would be objectivity. We tried to achieve this by describing the process of analysis. Using a large number of codes was preferred as opposed to starting with a condensation of the meaning units. Some material might then initially not correspond to the objective but the process made it possible for the author to pick up a large variation in the material at the early stage of analysis as suggested by the chosen method [88]. The author tried to stay as neutral as possible but in qualitative research one has to accept to be a part of the results [122]. In the later stages of the analysis during the work with categories the supervisor of the author was involved to create a consensus of the findings. Results and chosen quotes were then presented to the other co-authors.

Quantitative methods

The evaluation of HBB QIC was an observational study and its design offers some limitations. The main concern is that we can only describe the association between the intervention and its desired effect, not the actual causality. Also, the intervention was multi-faceted and made up of a package. We cannot unbundle the package to demonstrate the individual effect of its different parts on the outcomes. The implementation of the intervention was also performed in each unit supervised by the in-charge. Therefore, there might have been some variation in the nature of the final intervention between the units.

This was a case-referent study where 20% of the admitted mothers were selected to represent the characteristics of the whole population. Although the number of referents was large and the selection of them was randomized, there could have been some selection bias when women were included in the referent group. For example, a written consent was needed for inclusion. If the woman was illiterate, the consent was read to her. However, in such a situation the woman could have been more inclined to defer participation. Thus, the socio-economic status of the woman could have influenced the selection of referents.

The external validity of the results from the intervention should be considered when applying the results to other contexts. This was a hospital-based study in the capital city and when turning to district or community level the population and context targeted will be different. However, the weak system of perinatal and maternal surveillance in Nepal leaves hospital-based studies as one of the best choices so far. The extensive background data in our study can also be used in the future to compare populations, would HBB QIC be launched in other contexts within Nepal or in other low-income countries.

The lack of antenatal care among some of the women included in the study could have induced an under-reporting of maternal complications, as they were not known. This information bias could also have been incurred when health workers did not have the time to document steps that were taken during labor and delivery. There could also have been a performance bias in the study. Staff at the facility was aware about the ongoing study and it could have affected their work and decisions, e.g. the willingness to refer an infant to next level of care or withholding discharge and increasing monitoring. As blinding was not possible, health workers were also aware of whether a mother or infant belonged to the referent or case group.

Finally, attrition bias could have been a problem as neonatal deaths out of the hospital was not fully known. There was only telephone follow-up among the referent population. Any data on neonatal deaths after discharge

in the rest of the cohort was therefore not available. We cannot assume that neonatal deaths out of the hospital were systematic during the study because of the risk of performance bias discussed above.

We generally used logistic regression reporting odds ratios when calculating outcome probabilities. Although the concept of relative risk is easier to grasp, it is not appropriate to use if the incidence of a condition is not known. However, a general rule is that when the prevalence of a condition is below 10%, the relative risk and odds ratio will be approximately the same [123]. This was true for the main outcomes in our study. For comparisons of groups we typically used the chi square test for binary variables. If expected frequencies were below five we complemented the chi square test with Fisher exact test. T-test was used for comparisons of continuous variables. For ordinal variables we applied Wilcoxon rank-sum test [123].

The interpretation of the video material proved to be a challenge, especially when determining if the need for resuscitation was present. The time consuming process of watching all the videos and collecting data from them induced intra- and inter-rater bias. Collecting data from video recordings using image processing or recent advances in deep learning action classification could be an alternative in the future [79]. To our knowledge, no attempt to use such methods for video analysis has been applied in health care settings.

Health system implications

The feasibility of the HBB curriculum, along with its proven potential to reduce intrapartum stillbirth and neonatal mortality in low-income settings, set the stage for future large scale-up of training in neonatal resuscitation. After numerous trials, HBB has come to be the golden standard for such training, at a low cost. With the prevailing unacceptable rates of stillbirths and neonatal deaths globally, HBB will play a vital role in future efforts targeting this unfinished agenda. The quest for universal coverage of HBB and other low-cost and evidence-based interventions surrounding the time of birth in low-income settings must continue.

Quality of care and implementation strategies must also be addressed. The sustainability of acquired skills after clinical training is still a problem in various settings, and we have suggested a number of quality improvement strategies. We have also demonstrated that management involvement, both in quality development and in clinical audit and feedback, is crucial to arrive at robust changes in clinical skills going forward.

Finally, quality in the continuum of postnatal care must be improved to maintain improved survival at the time of birth following training in neonatal resuscitation. We have suggested exploring some of the programs available such as Essential Newborn Care or HBS. With better basic postnatal care in place, the time would also be right for investments in neonatal intensive care resources in low-income contexts, especially in terms of human resources.

Conclusions

- Health workers confirmed the importance of displaying protocols of neonatal resuscitation in order to have teams working in the same direction and to facilitate feedback
- Management in low-income situated contexts needs to address the way organizations deal with clinical incidents and initiate processes to learn from such audit
- Helping Babies Breathe implemented together with a Quality Improvement Cycle was effective to reduce intrapartum stillbirth and neonatal mortality on the first day of life in a low-income setting like Nepal
- Postnatal care needs to be strengthened in low-income situated facilities to maintain gains in neonatal survival on the day of delivery following training in neonatal resuscitation
- Pre-term and low birth weight infants in a low-income facility setting are not withheld resuscitation initiation and resuscitation of moderate pre-terms should not be deferred because of the low risk of long-term morbidity

Future perspectives

This thesis has generated answers related to the question of an effective implementation strategy for neonatal resuscitation training in low-income settings. However, new evidence usually generates new questions. From our findings, we suggest future research in this field and context to focus on the following areas listed below.

- Helping Babies Breathe implementation needs to be evaluated in a package together with interventions to improve quality of postnatal care
- Future study protocols of studies on neonatal mortality in facilities after training in neonatal resuscitation should include follow-up after the neonatal period to assess out of hospital mortality
- The long term mortality and morbidity outcomes after training in neonatal resuscitation should be explored along with cost-effectiveness analyses to map the full impact on society from such training
- The processing of data from video recordings of neonatal resuscitation needs to be developed if video is to be used as an effective tool for quality improvement
- The concept of quality improvement strategies when implementing training in neonatal resuscitation would benefit from further exploration, preferably also in district or community settings
- The effects on outcomes and sustainability of health worker skills in neonatal care from clinical audit should be evaluated in low-income settings

Summary

From 1990 to 2015 child mortality, defined as death occurring during the first five years of life, was reduced from 12.7 to 5.9 million globally. This accomplishment, fuelled by effectively addressing the most common causes of child mortality, cannot be underestimated. However, the reduction of neonatal mortality has not kept the same pace. Death during the first four weeks of life have continued to represent a growing part of child mortality and in 2015, 2.9 million lives were lost in the neonatal period. In addition to them, a total of 2.6 infants were stillborn. Stillbirth and neonatal mortality thus represent a large part of years of life lost due to disease and complications every year on our planet. The majority, or 99%, occur in low- and middle-income countries. Most of those infant deaths can be prevented with cheap and simple interventions such as better antenatal care for pregnant women; improved intrapartum surveillance; a clean delivery; early and exclusive breast-feeding; preventing the newborn infant from low body temperature; and treating infections. Approximately one tenth of all children born every year need some support to initiate breathing. The steps taken to help the newborn to establish its own breathing is called neonatal resuscitation and the method is usually simple and straightforward. For most non-breathing newborn infants the steps of drying, stimulating and applying ventilation with a bag-and-mask will be sufficient. Only a small fraction of infants born every year will need advanced care such as chest compressions, treatment with oxygen or medicines and continued mechanical ventilation.

In this thesis we describe a study at a maternity health facility in Kathmandu, Nepal. We arranged training in a simplified method for neonatal resuscitation training called Helping Babies Breathe developed by the American Academy of Pediatrics. Helping Babies Breathe is an educational package with pictorial charts and a simulation mannequin designed to be applied in low-income settings such as Nepal. All staff, including medical doctors, midwives and students at the facility was educated and we measured the outcome of stillbirth and death during the first period of life before and after training. To address the sustainability of acquired skills, we also introduced a cycle of quality improvement components with the training. After the intervention, stillborn children dying because of intrapartum complications was reduced by 54% and death of live born children during the first 24 hours was reduced by 49%. We also noted a prolonged survival during the neona-

tal period after the intervention. However, we also demonstrated that postnatal care for newborn infants was not sufficient to maintain the gains in survival on the day of delivery. Helping Babies Breathe was thus a feasible educational program with the potential to reduce newborn mortality in a low-income setting, but better quality of care after birth is also needed.

सारांश

विश्वभरमा सन १९९० देखि २०१५ को अवधिमा पाँच वर्षमुनिका बालबालिकाको मृत्युको संख्या प्रतिवर्ष एक करोड सत्ताईस लाख बाट झरेर उनानसाठी लाख पुगेको छ । पाँच वर्षमुनिका बाबबालिकाहरुमा हुने मृत्युका प्रमुख कारणहरुलाई सम्बोधन गरेर हाँसिल गरीएको यो उपलब्धीलाई कम आँक्न सकिन्न । तथापी नवजात शिशुको मृत्युदरमा भने सोही अनुरुपको सुधार भएको पाईंदैन । जन्मेको पहिलो चार हप्तामा हुने नवजात शिशुको मृत्युले अझैपनि बालमृत्युदरको ठुलो हिस्सा ओगटीरहेको छ । सन २०१५ मा मृत्यु भएका बालबालिकाहरु मध्ये २९ लाख नवजात शिशुहरु थिए । यसको अलावा सोही अवधिमा जम्मा छब्बिस लाख शिशुहरुको मृत जन्म भएको थियो । यसप्रकार मृत जन्म तथा नवजात शिशु मृत्युले प्रत्येक वर्ष संसारमा रोग र त्यसको जटिलताका कारणले हुने जीवन वर्षहरुको क्षती (years of life lost) को ठुलो हिस्सालाई प्रतिनिधित्व गरिरहेको छ । जम्मा नवजात शिशुको मृत्यु मध्ये धेरैजसो मृत्यु (९९ प्रतिशत) न्यून र मध्यम आय भएका राष्ट्रहरुमा हुने गरेको छ । धेरैजसो नवजात शिशुको मृत्युलाई सजिलो र साधारण क्रियाकलापहरुबाट रोक्न सकिन्छ जस्तै उपयुक्त पूर्व प्रसूति सेवा दिने, गर्भवती र प्रसूतिको समयमा उचित निगरानी गर्ने, सफा र सुरक्षित प्रसूति गराउने, शिशु जन्मेपछि छिटो र ६ महिनासम्म स्तनपानमात्र गराउने, नवजात शिशुलाई कम तापक्रम हुनबाट बचाउने र संक्रमणको उपचार गर्ने । प्रत्येक वर्ष जन्मीएका मध्ये लगभग १० प्रतिशत नवजात शिशुलाई श्वासप्रश्वास प्रकृया शुरुवात गर्नका लागि केही सहयोगको आवश्यकता पर्दछ । नवजात शिशुलाई आफैं सास फेर्न सहयोग गर्न अपनाईने प्रकृयालाई नवजात शिशु श्वासप्रश्वास सहयोगी भनिन्छ जुन प्राय गरेर सजिलो र सिधा प्रकृया हो । धेरैजसो शिशुहरुका लागि जन्मनासाथ सुक्खा बनाउने, सुम्सुम्याउने तथा ब्याग र मास्कको प्रयोग गरी कृत्रिम श्वासप्रश्वास दिने चरणहरुनै श्वासप्रश्वासमा सहयोग गर्न पर्याप्त हुन्छन् । केवल थोरै संख्यामा मात्र शिशुहरुको लागि विशिष्ट सेवा जस्तै चेष्ट कम्प्रेशन, अक्सिजन दिएर गरिने उपचार अथवा निरन्तर यान्त्रिक श्वासप्रश्वास को आवश्यकता पर्दछ ।

यस शोधग्रन्थ (थेसिस) मा नेपालको राजधानी काठमांडौको एउटा अस्पतालमा गरिएको अध्ययनलाई व्याख्या गरिएको छ । हामिले यस अध्ययनका लागि अमेरिकी बालरोग विशेषज्ञहरुको संस्था (अमेरिकन एकाडेमी अफ पेडियाट्रिक्स) ले विकास गरेको शिशु श्वास प्रश्वास सहयोगी मा आधारित रहेर नवजात शिशुलाई श्वासप्रश्वासमा सहयोग गर्ने प्रकृयाको तालिम स्वास्थ्यकर्मीहरुलाई दिएका थियौं । ***शिशु श्वास प्रश्वास सहयोगी*** चित्रबाट वर्णन गरिएको चार्ट तथा अभ्यास गर्ने डमी (मेनीकिन) सहितको शैक्षिक/तालिम प्याकेज हो जुन नेपाल जस्तो न्यून आय भएका राष्ट्रहरुमा उपयोग गर्न सकिने ढंगले विकास गरिएको छ । पहिलो चरणमा अस्पतालका सबै स्वास्थ्यकर्मी (मेडिकल अफिसर, मिडवाईफ) तथा अस्पतालमा अभ्यासका लागि आएका विद्यार्थीहरुलाई शिशु श्वासप्रश्वास सहयोगीको प्रकृयाको तालिम दिईएको थियो । त्यसपश्चात तालिम अघि र तालिम पछिको मृत जन्म र जीवनको पहिलो अवधिमा हुने मृत्यु को नतिजालाई मुल्याङ्कन गरिएको थियो । सिकेका सीपहरुको दिगोपनाको लागि हामिले गुणस्तर सुधारका चक्रका भागहरुलाई पनि तालिम प्याकेजमा समावेश गरेका थियौं । यस क्रियाकलाप पश्चात गर्भ तथा प्रसूतिको जटिलताको कारणले हुने मृत जन्ममा ५४ प्रतिशत तथा जिवित नवजात शिशुहरुमा जन्मेको २४ घण्टा भित्रमा हुने मृत्युमा ४९ प्रतिशतले कमी आएको पाईएको थियो । यस क्रियाकलापपश्चात नवजात शिशु अवस्थामा लामो समयसम्म जीवित रहने सम्भावना पनि बढेर गएको पाईयो । तथापी शिशु जन्मेको दिनमा आर्जित उपलब्धीलाई कायम गरीराख्नका लागि नवजात शिशुहरुलाई प्रसूति पछि आवश्यक पर्ने स्याहार पर्याप्त नभएको पाईयो । यसप्रकार शिशु श्वासप्रश्वास सहयोगी न्यून आय भएका राष्ट्रहरुमा नवजात शिशु मृत्यु घटाउनका लागि उपयोगी तालिम/शैक्षिक कार्यक्रम रहेको पाईएको छ तर यसको साथमा शिशुलाई जन्मपश्चात गुणस्तरीय स्याहारको पनि आवश्यकता पर्दछ ।

Acknowledgements

First of all, I direct gratitude to my supervisors. Mats Målqvist for his brilliant main supervision, always present and available (although not in person but on-line!), delicately challenging and supporting me at the same time. The future is yours in this field, my friend. Margareta Larsson for your excellent contributions to my qualitative work and my understanding of the everyday situation for midwives globally. Uwe Ewald for your vast knowledge in neonatology and research design. The three of you made all the difference for my doctoral studies.

There would have been no study without the participants in Nepal. Thanks to all mothers, infants and their families who decided to join the trial. Nepal, with its resilient, humble and kind people, has a bright future, I am sure!

Thank you, Ashish KC, the energetic and ambitious principal investigator of the project who also became a close friend. Without your exceptional efforts, I would never have been able to complete. My deepest gratitude to you and your family for your hospitality during visits to Nepal.

I am very grateful to the Paropakar Maternity and Women´s Hospital for providing a study site and support to the research team. The hospital director, administrative staff, medical doctors, nurses, students and supervisors all made great contributions to our common work. Also, the collaboration with Ministry of Health in Nepal and the Midwife Society of Nepal was very important. Special thanks to the nurse midwives who opened their hearts and shared their perceptions of teamwork at the facility during focus group discussions.

So many Nepali co-workers provided invaluable support at the study site. Special thanks to Ravi Vitrakoti for excellent coordination; Kedar Baral for input to focus groups and the introduction to a progressive alternative in medical education; Sabitri Devkota for excellent focus group moderation; the surveillance officers for their enormous efforts in data collection; Nisha Rana for quick replies on data details; and Omkar Basnet for his kind support when working in Nepal.

I thank my colleagues of medical doctors, nurses, physiotherapists, occupational therapists, psychologists and administrative staff at the children´s hospital in Uppsala. The work you provide for the children of our county and beyond cannot be underestimated and inspired me to further studies in medicine. I provide special thanks to Christina Krantz for clinical supervision and Linda Wallström who introduced me to neonatal resuscitation back in 2011.

My managers at the hospital, Christophe Pedroletti and Johan Kaarme, who have provided the possibility of leave from clinical work to complete this thesis. Your support to co-workers who strive for doctoral studies and research will pay off in the future development of pediatric specialist care at our clinic. I also thank our management administrators, Krisztina and Maria.

The administrative staff at International Maternal and Children´s Health at Uppsala University who provided all support needed in terms of working place, financial support, paper work, insurance and IT services; Jenny, Karin, Kristine, Hanna A and T, Christina, Andreas and Linda. Anna Axell for keeping my back in shape during long hours of office work that my body was not made for, and Linda for maintaining my room neat and tidy. I also thank all staff at the department of Women´s and Children´s Health, especially Agneta Skoog-Svanberg and Martin Selinus.

Thank you all researchers and PhD students at the department. I may not have been around as much as I wanted to, but our meetings, collaborative groups, research seminars and lunch discussions meant a lot to me. And the fredagsfika! It is a true gift to be part of the global melting pot of various professionals at IMCH and I have learned many things from all of you. Thanks also to all students attending the master course over the years, for sharing your literature reviews and actively listening to lectures.

Many other Swedish collaborators contributed to the work for this thesis. Especially Camilla Zetterlund for the work on Paper IV; Caroline Lindbäck for your piloting of the video material; and Ola Andersson for the introduction to the wonderful world of cord-clamping and for kicking off my statistical analyses at the International Club, Kathmandu.

Aileen Ireland provided fast and reliable English proofreading that I am very grateful for.

Many thanks to the funders of the study; Laerdal Foundation of Acute Medicine, Latter Day Saints Charities, Svenska Läkaresällskapet and Vetenskapsrådet.

Eakman Pariyar, dear friend of my family, who took us to his Gorkha village of Darbung to experience the happiness and hardships of Nepali community life. Your compassion for improving the situation of the school children in Darbung is a fantastic thing we can all learn from.

To my faithful friend Lars Davås for challenging my world views when we meet.

I thank my mum and dad for all their love and appreciation during hard work. My children are lucky to have many primary caretakers, not just two. I must also thank you for providing me with the feasible genetic material to complete this journey! Thanks to my dear brother, who provided an example with his hard academic work over-seas. I am sorry I stole your first name initial on PubMed! I just wish we could see more of each other. I am indebted forever to my brother-in-law and close friend, Andreas Karlsson. If it weren't for those dreadful moments in basic military service back in the nineties, I would be another person today. When looking back, my thoughts also go to Ghislaine. I wish you didn´t have to leave us so early. My gratitude also goes to my father- and mother-in-law, for encouragement and for having such wonderful children.

Finally, thanks to my beloved wife and children. Anna, Ville and Viggo: you provide the rationale for everything else I fill my life with. I am so grateful to be blessed with a family who share my curiosity for our beautiful and challenging world, and the desire to explore it.

References

1. Assembly UNG: **United Nations Millennium Declaration**. In. New York: United Nations; 2000.
2. You D, Hug L, Ejdemyr S, Idele P, Hogan D, Mathers C, Gerland P, New JR, Alkema L, United Nations Inter-agency Group for Child Mortality E: **Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-agency Group for Child Mortality Estimation**. *Lancet* 2015, **386**(10010):2275-2286.
3. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, Lalli M, Bhutta Z, Barros AJ, Christian P *et al*: **Every Newborn: progress, priorities, and potential beyond survival**. *Lancet* 2014, **384**(9938):189-205.
4. Kinney MV, Cocoman O, Dickson KE, Daelmans B, Zaka N, Rhoda NR, Moxon SG, Kak L, Lawn JE, Khadka N *et al*: **Implementation of the Every Newborn Action Plan: Progress and lessons learned**. *Seminars in perinatology* 2015, **39**(5):326-337.
5. You D, Wardlaw T, Newby H, Anthony D, Rogers K: **Renewing the promise of survival for children**. *Lancet* 2013, **382**(9897):1002-1004.
6. Grove J, Claeson M, Bryce J, Amouzou A, Boerma T, Waiswa P, Victora C, Kirkland G: **Maternal, newborn, and child health and the Sustainable Development Goals--a call for sustained and improved measurement**. *Lancet* 2015, **386**(10003):1511-1514.
7. Organization WH: **Neonatal and perinatal mortality: country, regional and global estimates**. In. Geneva; 2006.
8. Bhutta ZA, Lassi ZS, Blanc A, Donnay F: **Linkages among reproductive health, maternal health, and perinatal outcomes**. *Seminars in perinatology* 2010, **34**(6):434-445.
9. Jamison DT: **Incorporating Dearths near the time of birth into estimates of the global burden of disease**. Washington DC: The World Bank; 2006.
10. Wang H, Liddell CA, Coates MM, Mooney MD, Levitz CE, Schumacher AE, Apfel H, Iannarone M, Phillips B, Lofgren KT *et al*: **Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013**. *Lancet* 2014, **384**(9947):957-979.
11. Froen JF, Friberg IK, Lawn JE, Bhutta ZA, Pattinson RC, Allanson ER, Flenady V, McClure EM, Franco L, Goldenberg RL *et al*: **Stillbirths: progress and unfinished business**. *Lancet* 2016, **387**(10018):574-586.
12. Blencowe H, Cousens S, Jassir FB, Say L, Chou D, Mathers C, Hogan D, Shiekh S, Qureshi ZU, You D *et al*: **National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis**. *Lancet Glob Health* 2016, **4**(2):e98-e108.

13. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, Flenady V, Froen JF, Qureshi ZU, Calderwood C *et al*: **Stillbirths: rates, risk factors, and acceleration towards 2030**. *Lancet* 2016, **387**(10018):587-603.
14. Cousens S, Blencowe H, Stanton C, Chou D, Ahmed S, Steinhardt L, Creanga AA, Tuncalp O, Balsara ZP, Gupta S *et al*: **National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis**. *Lancet* 2011, **377**(9774):1319-1330.
15. Lawn JE, Yakoob MY, Haws RA, Soomro T, Darmstadt GL, Bhutta ZA: **3.2 million stillbirths: epidemiology and overview of the evidence review**. *BMC pregnancy and childbirth* 2009, **9 Suppl 1**:S2.
16. **Surviving the first day** [https://www.savethechildren.net/article/surviving-first-day]
17. Darmstadt GL, Kinney MV, Chopra M, Cousens S, Kak L, Paul VK, Martines J, Bhutta ZA, Lawn JE, Lancet Every Newborn Study G: **Who has been caring for the baby?** *Lancet* 2014, **384**(9938):174-188.
18. Oza S, Lawn JE, Hogan DR, Mathers C, Cousens SN: **Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000-2013**. *Bulletin of the World Health Organization* 2015, **93**(1):19-28.
19. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, Rudan I, Campbell H, Cibulskis R, Li M *et al*: **Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000**. *Lancet* 2012, **379**(9832):2151-2161.
20. Miller SP, Latal B, Clark H, Barnwell A, Glidden D, Barkovich AJ, Ferriero DM, Partridge JC: **Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy**. *American journal of obstetrics and gynecology* 2004, **190**(1):93-99.
21. Hankins GD, Speer M: **Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy**. *Obstetrics and gynecology* 2003, **102**(3):628-636.
22. Maulik PK, Darmstadt GL: **Childhood disability in low- and middle-income countries: overview of screening, prevention, services, legislation, and epidemiology**. *Pediatrics* 2007, **120 Suppl 1**:S1-55.
23. Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, Chou D, Say L, Modi N, Katz J *et al*: **Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010**. *Pediatric research* 2013, **74 Suppl 1**:17-34.
24. Marlow N: **Full term; an artificial concept**. *Archives of disease in childhood Fetal and neonatal edition* 2012, **97**(3):F158-159.
25. Lee AC, Kozuki N, Blencowe H, Vos T, Bahalim A, Darmstadt GL, Niermeyer S, Ellis M, Robertson NJ, Cousens S *et al*: **Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990**. *Pediatric research* 2013, **74 Suppl 1**:50-72.
26. Spector JM, Daga S: **Preventing those so-called stillbirths**. *Bulletin of the World Health Organization* 2008, **86**(4):315-316.
27. Goldenberg RL, McClure EM, Jobe AH, Kamath-Rayne BD, Gravette MG, Rubens CE: **Stillbirths and neonatal mortality as outcomes**. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2013, **123**(3):252-253.

28. Lee AC, Cousens S, Wall SN, Niermeyer S, Darmstadt GL, Carlo WA, Keenan WJ, Bhutta ZA, Gill C, Lawn JE: **Neonatal resuscitation and immediate newborn assessment and stimulation for the prevention of neonatal deaths: a systematic review, meta-analysis and Delphi estimation of mortality effect**. *BMC public health* 2011, **11 Suppl 3**:S12.
29. Lawn JE, Lee AC, Kinney M, Sibley L, Carlo WA, Paul VK, Pattinson R, Darmstadt GL: **Two million intrapartum-related stillbirths and neonatal deaths: where, why, and what can be done?** *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2009, **107 Suppl 1**:S5-18, S19.
30. Mondal D, Galloway TS, Bailey TC, Mathews F: **Elevated risk of stillbirth in males: systematic review and meta-analysis of more than 30 million births**. *BMC medicine* 2014, **12**:220.
31. Nielsen BB, Liljestrand J, Hedegaard M, Thilsted SH, Joseph A: **Reproductive pattern, perinatal mortality, and sex preference in rural Tamil Nadu, south India: community based, cross sectional study**. *BMJ* 1997, **314**(7093):1521-1524.
32. Carlo W: **Effect of Essential Newborn Care (ENC) Training: A global network study of site differences**. In. Honolulu; 2009.
33. Arregoces L, Daly F, Pitt C, Hsu J, Martinez-Alvarez M, Greco G, Mills A, Berman P, Borghi J: **Countdown to 2015: changes in official development assistance to reproductive, maternal, newborn, and child health, and assessment of progress between 2003 and 2012**. *Lancet Glob Health* 2015, **3**(7):e410-421.
34. Darmstadt GL, Bhutta ZA, Cousens S, Adam T, Walker N, de Bernis L, Lancet Neonatal Survival Steering T: **Evidence-based, cost-effective interventions: how many newborn babies can we save?** *Lancet* 2005, **365**(9463):977-988.
35. te Pas AB, Davis PG, Hooper SB, Morley CJ: **From liquid to air: breathing after birth**. *The Journal of pediatrics* 2008, **152**(5):607-611.
36. Kattwinkel J, Niermeyer S, Nadkarni V, Tibballs J, Phillips B, Zideman D, Van Reempts P, Osmond M: **Resuscitation of the newly born infant: an advisory statement from the Pediatric Working Group of the International Liaison Committee on Resuscitation**. *European journal of pediatrics* 1999, **158**(4):345-358.
37. Wall SN, Lee AC, Niermeyer S, English M, Keenan WJ, Carlo W, Bhutta ZA, Bang A, Narayanan I, Ariawan I *et al*: **Neonatal resuscitation in low-resource settings: what, who, and how to overcome challenges to scale up?** *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2009, **107 Suppl 1**:S47-62, S63-44.
38. Kattwinkel J: **Neonatal resuscitation guidelines for ILCOR and NRP: evaluating the evidence and developing a consensus**. *Journal of perinatology : official journal of the California Perinatal Association* 2008, **28 Suppl 3**:S27-29.
39. Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, Simon WM, Weiner GM, Zaichkin JG: **Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care**. *Circulation* 2015, **132**(18 Suppl 2):S543-560.
40. Saugstad OD: **The role of oxygen in neonatal resuscitation**. *Clinics in perinatology* 2004, **31**(3):431-443.

41. Rabi Y, Rabi D, Yee W: **Room air resuscitation of the depressed newborn: a systematic review and meta-analysis**. *Resuscitation* 2007, **72**(3):353-363.
42. Singhal N, Lockyer J, Fidler H, Keenan W, Little G, Bucher S, Qadir M, Niermeyer S: **Helping Babies Breathe: global neonatal resuscitation program development and formative educational evaluation**. *Resuscitation* 2012, **83**(1):90-96.
43. Niermeyer S: **From the Neonatal Resuscitation Program to Helping Babies Breathe: Global impact of educational programs in neonatal resuscitation**. *Seminars in fetal & neonatal medicine* 2015, **20**(5):300-308.
44. Niermeyer S: **Ventilation Remains the Key to Neonatal Resuscitation**. *The Journal of pediatrics* 2016, **171**:8-10.
45. Msemo G, Massawe A, Mmbando D, Rusibamayila N, Manji K, Kidanto HL, Mwizamuholya D, Ringia P, Ersdal HL, Perlman J: **Newborn mortality and fresh stillbirth rates in Tanzania after helping babies breathe training**. *Pediatrics* 2013, **131**(2):e353-360.
46. Goudar SS, Somannavar MS, Clark R, Lockyer JM, Revankar AP, Fidler HM, Sloan NL, Niermeyer S, Keenan WJ, Singhal N: **Stillbirth and newborn mortality in India after helping babies breathe training**. *Pediatrics* 2013, **131**(2):e344-352.
47. Hoban R, Bucher S, Neuman I, Chen M, Tesfaye N, Spector JM: **'Helping babies breathe' training in sub-saharan Africa: educational impact and learner impressions**. *Journal of tropical pediatrics* 2013, **59**(3):180-186.
48. **Helping Babies Breathe 2nd edition**
49. Boyle RJ, McIntosh N: **Ethical considerations in neonatal resuscitation: clinical and research issues**. *Seminars in neonatology : SN* 2001, **6**(3):261-269.
50. Airede KI: **Should we resuscitate? Ethical dilemmas**. *Annals of tropical paediatrics* 1991, **11**(2):169-174.
51. Deorari AK, Paul VK, Singh M, Vidyasagar D, Medical Colleges N: **Impact of education and training on neonatal resuscitation practices in 14 teaching hospitals in India**. *Annals of tropical paediatrics* 2001, **21**(1):29-33.
52. Haines A, Kuruvilla S, Borchert M: **Bridging the implementation gap between knowledge and action for health**. *Bulletin of the World Health Organization* 2004, **82**(10):724-731; discussion 732.
53. Althabe F, Bergel E, Cafferata ML, Gibbons L, Ciapponi A, Aleman A, Colantonio L, Palacios AR: **Strategies for improving the quality of health care in maternal and child health in low- and middle-income countries: an overview of systematic reviews**. *Paediatric and perinatal epidemiology* 2008, **22 Suppl 1**:42-60.
54. Gelbart B, Hiscock R, Barfield C: **Assessment of neonatal resuscitation performance using video recording in a perinatal centre**. *Journal of paediatrics and child health* 2010, **46**(7-8):378-383.
55. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L *et al*: **Effectiveness and efficiency of guideline dissemination and implementation strategies**. *Health Technol Assess* 2004, **8**(6):iii-iv, 1-72.
56. Musafili A, Essen B, Baribwira C, Rukundo A, Persson LA: **Evaluating Helping Babies Breathe: training for healthcare workers at hospitals in Rwanda**. *Acta Paediatr* 2013, **102**(1):e34-38.
57. Skidmore MB, Urquhart H: **Retention of skills in neonatal resuscitation**. *Paediatrics & child health* 2001, **6**(1):31-35.

58. Kaczorowski J, Levitt C, Hammond M, Outerbridge E, Grad R, Rothman A, Graves L: **Retention of neonatal resuscitation skills and knowledge: a randomized controlled trial**. *Family medicine* 1998, **30**(10):705-711.
59. Carlo WA, Wright LL, Chomba E, McClure EM, Carlo ME, Bann CM, Collins M, Harris H: **Educational impact of the neonatal resuscitation program in low-risk delivery centers in a developing country**. *The Journal of pediatrics* 2009, **154**(4):504-508 e505.
60. Ersdal HL, Vossius C, Bayo E, Mduma E, Perlman J, Lippert A, Soreide E: **A one-day "Helping Babies Breathe" course improves simulated performance but not clinical management of neonates**. *Resuscitation* 2013, **84**(10):1422-1427.
61. Madon T, Hofman KJ, Kupfer L, Glass RI: **Public health. Implementation science**. *Science* 2007, **318**(5857):1728-1729.
62. Bergstrom A, Peterson S, Namusoko S, Waiswa P, Wallin L: **Knowledge translation in Uganda: a qualitative study of Ugandan midwives' and managers' perceived relevance of the sub-elements of the context cornerstone in the PARIHS framework**. *Implementation science : IS* 2012, **7**:117.
63. Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S, Robertson N, Wensing M, Fiander M, Eccles MP *et al*: **Tailored interventions to address determinants of practice**. *Cochrane Database Syst Rev* 2015(4):CD005470.
64. McCoy D, Storeng K, Filippi V, Ronsmans C, Osrin D, Borchert M, Campbell OM, Wolfe R, Prost A, Hill Z *et al*: **Maternal, neonatal and child health interventions and services: moving from knowledge of what works to systems that deliver**. *Int Health* 2010, **2**(3):228.
65. Rycroft-Malone J, Kitson A, Harvey G, McCormack B, Seers K, Titchen A, Estabrooks C: **Ingredients for change: revisiting a conceptual framework**. *Quality & safety in health care* 2002, **11**(2):174-180.
66. McCormack B, Kitson A, Harvey G, Rycroft-Malone J, Titchen A, Seers K: **Getting evidence into practice: the meaning of 'context'**. *Journal of advanced nursing* 2002, **38**(1):94-104.
67. Rowe AK, de Savigny D, Lanata CF, Victora CG: **How can we achieve and maintain high-quality performance of health workers in low-resource settings?** *Lancet* 2005, **366**(9490):1026-1035.
68. Forsetlund L, Bjorndal A, Rashidian A, Jamtvedt G, O'Brien MA, Wolf F, Davis D, Odgaard-Jensen J, Oxman AD: **Continuing education meetings and workshops: effects on professional practice and health care outcomes**. *Cochrane Database Syst Rev* 2009(2):CD003030.
69. ten Hoope-Bender P, de Bernis L, Campbell J, Downe S, Fauveau V, Fogstad H, Homer CS, Kennedy HP, Matthews Z, McFadden A *et al*: **Improvement of maternal and newborn health through midwifery**. *Lancet* 2014, **384**(9949):1226-1235.
70. Nelson CA, Spector JM: **Neonatal resuscitation capacity in Nepal**. *Journal of paediatrics and child health* 2011, **47**(3):83-86.
71. Simmons D, Sherwood G: **Neonatal intensive care unit and emergency department nurses' descriptions of working together: building team relationships to improve safety**. *Critical care nursing clinics of North America* 2010, **22**(2):253-260.
72. Filby A, McConville F, Portela A: **What Prevents Quality Midwifery Care? A Systematic Mapping of Barriers in Low and Middle Income Countries from the Provider Perspective**. *PloS one* 2016, **11**(5):e0153391.

73. Bream KD, Gennaro S, Kafulafula U, Mbweza E, Hehir D: **Barriers to and facilitators for newborn resuscitation in Malawi, Africa**. *Journal of midwifery & women's health* 2005, **50**(4):329-334.
74. Lawn JE, Bahl R, Bergstrom S, Bhutta ZA, Darmstadt GL, Ellis M, English M, Kurinczuk JJ, Lee AC, Merialdi M *et al*: **Setting research priorities to reduce almost one million deaths from birth asphyxia by 2015**. *PLoS medicine* 2011, **8**(1):e1000389.
75. Oakley E, Stocker S, Staubli G, Young S: **Using video recording to identify management errors in pediatric trauma resuscitation**. *Pediatrics* 2006, **117**(3):658-664.
76. Peltier LF, Geertsma RH, Youmans RL: **Television videotape recording: an adjunct in teaching emergency medical care**. *Surgery* 1969, **66**(1):233-236.
77. Carbine DN, Finer NN, Knodel E, Rich W: **Video recording as a means of evaluating neonatal resuscitation performance**. *Pediatrics* 2000, **106**(4):654-658.
78. Lindback C, Kc A, 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.
79. Ren S, He K, Girshick R, Sun J: **Faster R-CNN: Towards Real-Time Object Detection with Region Proposal Networks**. *IEEE Trans Pattern Anal Mach Intell* 2016.
80. Programme UND: **Human Development Report 2013, The Rise of the South, Human Progress in Diverse World**. In: *Human Development Report 2013*. New York, USA: UNDP; 2013.
81. Ministry of Health and Population DoHS, Family Health Division: **Female Community Health Volunteer Revised Strategy**. In. Kathmandu, Nepal: Ministry of Health and Population, Department of Health Services, Family Health Division; 2010.
82. Pradhan YV, Upreti SR, Pratap KCN, K CA, Khadka N, Syed U, Kinney MV, Adhikari RK, Shrestha PR, Thapa K *et al*: **Newborn survival in Nepal: a decade of change and future implications**. *Health policy and planning* 2012, **27 Suppl 3**:iii57-71.
83. Ashish KC, Malqvist M, Wrammert J, Verma S, Aryal DR, Clark R, Naresh PK, Vitrakoti R, Baral K, Ewald U: **Implementing a simplified neonatal resuscitation protocol-helping babies breathe at birth (HBB) - at a tertiary level hospital in Nepal for an increased perinatal survival**. *BMC pediatrics* 2012, **12**:159.
84. Ministry of Health and Population GoN: **Annual Report "Smarika" 2068/69**. In. Kathmandu, Nepal: Paropakar Maternity and Women's Hospital; 2011/12.
85. Plsek PE: **Quality improvement methods in clinical medicine**. *Pediatrics* 1999, **103**(1 Suppl E):203-214.
86. van Teijlingen E, Pitchforth E: **Focus group research in family planning and reproductive health care**. *The journal of family planning and reproductive health care / Faculty of Family Planning & Reproductive Health Care, Royal College of Obstetricians & Gynaecologists* 2006, **32**(1):30-32.
87. Tang KC, Davis A: **Critical factors in the determination of focus group size**. *Fam Pract* 1995, **12**(4):474-475.
88. Graneheim UH, Lundman B: **Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness**. *Nurse education today* 2004, **24**(2):105-112.

89. **Low Birthweight: Country, regional and global estimates** [https://es.scribd.com/document/191071127/Low-Birthweight-From-EY]
90. Blanc AK, Wardlaw T: **Monitoring low birth weight: an evaluation of international estimates and an updated estimation procedure**. *Bulletin of the World Health Organization* 2005, **83**(3):178-185.
91. Barnard J, Meng XL: **Applications of multiple imputation in medical studies: from AIDS to NHANES**. *Stat Methods Med Res* 1999, **8**(1):17-36.
92. Bould MD, Hayter MA, Campbell DM, Chandra DB, Joo HS, Naik VN: **Cognitive aid for neonatal resuscitation: a prospective single-blinded randomized controlled trial**. *British journal of anaesthesia* 2009, **103**(4):570-575.
93. Jamtvedt G, Young JM, Kristoffersen DT, O'Brien MA, Oxman AD: **Audit and feedback: effects on professional practice and health care outcomes**. *Cochrane Database Syst Rev* 2006(2):CD000259.
94. Ahluwalia J, Marriott L: **Critical incident reporting systems**. *Seminars in fetal & neonatal medicine* 2005, **10**(1):31-37.
95. Pattinson RC, Say L, Makin JD, Bastos MH: **Critical incident audit and feedback to improve perinatal and maternal mortality and morbidity**. *Cochrane Database Syst Rev* 2005(4):CD002961.
96. Pham JC, Girard T, Pronovost PJ: **What to do with healthcare incident reporting systems**. *J Public Health Res* 2013, **2**(3):e27.
97. Pirkle CM, Dumont A, Zunzunegui MV: **Criterion-based clinical audit to assess quality of obstetrical care in low- and middle-income countries: a systematic review**. *International journal for quality in health care : journal of the International Society for Quality in Health Care / ISQua* 2011, **23**(4):456-463.
98. Walker DM, Cohen SR, Fritz J, Olvera-Garcia M, Zelek ST, Fahey JO, Romero-Martinez M, Montoya-Rodriguez A, Lamadrid-Figueroa H: **Impact Evaluation of PRONTO Mexico: A Simulation-Based Program in Obstetric and Neonatal Emergencies and Team Training**. *Simulation in healthcare : journal of the Society for Simulation in Healthcare* 2016, **11**(1):1-9.
99. Bang A, Patel A, Bellad R, Gisore P, Goudar SS, Esamai F, Liechty EA, Meleth S, Goco N, Niermeyer S *et al*: **Helping Babies Breathe (HBB) training: What happens to knowledge and skills over time?** *BMC pregnancy and childbirth* 2016, **16**(1):364.
100. KC A, Wrammert J, Nelin V, Ewald U, Clark R, Peterson S, Målqvist M: **Evaluation of Helping Babies Breathe Quality Improvement Cycle (HBB-QIC) on retention of neonatal resuscitation skills six months after training in a low-income setting like Nepal**. Manuscript; 2016.
101. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L *et al*: **National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications**. *Lancet* 2012, **379**(9832):2162-2172.
102. Seale AC, Blencowe H, Zaidi A, Ganatra H, Syed S, Engmann C, Newton CR, Vergnano S, Stoll BJ, Cousens SN *et al*: **Neonatal severe bacterial infection impairment estimates in South Asia, sub-Saharan Africa, and Latin America for 2010**. *Pediatric research* 2013, **74 Suppl 1**:73-85.

103. Bang A, Bellad R, Gisore P, Hibberd P, Patel A, Goudar S, Esamai F, Goco N, Meleth S, Derman RJ *et al*: **Implementation and evaluation of the Helping Babies Breathe curriculum in three resource limited settings: does Helping Babies Breathe save lives? A study protocol**. *BMC pregnancy and childbirth* 2014, **14**:116.
104. **Helping Babies Survive** [aap.org]
105. Thukral A, Lockyer J, Bucher SL, Berkelhamer S, Bose C, Deorari A, Esamai F, Faremo S, Keenan WJ, McMillan D *et al*: **Evaluation of an educational program for essential newborn care in resource-limited settings: Essential Care for Every Baby**. *BMC pediatrics* 2015, **15**:71.
106. Kc A, Wrammert J, Clark RB, Ewald U, Vitrakoti R, Chaudhary P, Pun A, Raaijmakers H, Malqvist M: **Reducing Perinatal Mortality in Nepal Using Helping Babies Breathe**. *Pediatrics* 2016, **137**(6).
107. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, Kinney M, Lawn J, Born Too Soon Preterm Birth Action G: **Born too soon: the global epidemiology of 15 million preterm births**. *Reproductive health* 2013, **10 Suppl 1**:S2.
108. Lachman P, Jayadev A, Rahi M: **The case for quality improvement in the Neonatal Intensive Care Unit**. *Early human development* 2014, **90**(11):719-723.
109. Zeitlin J, Manktelow BN, Piedvache A, Cuttini M, Boyle E, van Heijst A, Gadzinowski J, Van Reempts P, Huusom L, Weber T *et al*: **Use of evidence based practices to improve survival without severe morbidity for very preterm infants: results from the EPICE population based cohort**. *BMJ* 2016, **354**:i2976.
110. Shah PS, Lee SK, Lui K, Sjors G, Mori R, Reichman B, Hakansson S, Feliciano LS, Modi N, Adams M *et al*: **The International Network for Evaluating Outcomes of very low birth weight, very preterm neonates (iNeo): a protocol for collaborative comparisons of international health services for quality improvement in neonatal care**. *BMC pediatrics* 2014, **14**:110.
111. Chawla D, Suresh GK: **Quality improvement in neonatal care - a new paradigm for developing countries**. *Indian journal of pediatrics* 2014, **81**(12):1367-1372.
112. Pin TW, Eldridge B, Galea MP: **A review of developmental outcomes of term infants with post-asphyxia neonatal encephalopathy**. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society* 2009, **13**(3):224-234.
113. Ellis M, Shrestha L, Shrestha PS, Manandhar DS, Bolam AJ, AM LC: **Clinical predictors of outcome following mild and moderate neonatal encephalopathy in term newborns in Kathmandu, Nepal**. *Acta Paediatr* 2001, **90**(3):316-322.
114. Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteno CD, Malan AF: **The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome**. *Acta Paediatr* 1997, **86**(7):757-761.
115. Beardsley MC: **Aesthetics**. New York,: Harcourt; 1958.
116. Charmaz K: **Constructing grounded theory**. London ; Thousand Oaks, Calif.: Sage Publications; 2006.
117. Peterson-Sweeney K: **The use of focus groups in pediatric and adolescent research**. *J Pediatr Health Care* 2005, **19**(2):104-110.

118. Mays N, Pope C: **Rigour and qualitative research**. *BMJ* 1995, **311**(6997):109-112.
119. Suen LJ, Huang HM, Lee HH: **[A comparison of convenience sampling and purposive sampling]**. *Hu li za zhi The journal of nursing* 2014, **61**(3):105-111.
120. Kitzinger J: **Qualitative research. Introducing focus groups**. *BMJ* 1995, **311**(7000):299-302.
121. Forman J, Creswell JW, Damschroder L, Kowalski CP, Krein SL: **Qualitative research methods: key features and insights gained from use in infection prevention research**. *American journal of infection control* 2008, **36**(10):764-771.
122. Boyd CO: **Philosophical foundations of qualitative research**, vol. 19-2535. ny: NLN Publications; 1993.
123. Campbell M: **Medical Statistics**. West Sussex, England; 2007.

Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1308

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-316728

ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2017