Supporting neonatal resuscitation in low-resource settings

Innovations and new strategies

Susanna Myrnerts Höök

Thesis for the degree of Philosophiae Doctor (PhD)
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To all midwives in low-resource settings

Acknowledgements

I dedicate this thesis to *all midwives in low-resource settings* who yearly take care of millions of neonates without support from functioning health systems, advanced monitoring equipment, adequate medicines and doctors, and with low salaries - often not enough to support their families. Your daily struggle makes this world a better place.

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With the kind permission of the illustrator, Anna Lindsten.

The scientific environment

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Abbreviations

AE	Adverse Event
aEEG	Amplitude-integrated ElectroEncephaloGram
bpm	Beats Per Minute
CISMAC	Centre for Intervention Science in Maternal and Child Health
CoSTR	Consensus on Sciences with Treatment Recommendations
CPR	CardioPulmonary Resuscitation
CRF	Case Report Form
ECG	ElectroCardioGraphy
ETT	EndoTracheal Tube
FM	Face Mask
FMV	Face-Mask Ventilation
HBB	Helping Babies Breathe
HBS	Helping Babies Survive
HIE	Hypoxic-Ischemic Encephalopathy
HR	Heart Rate
IDMC	Independent Data Monitoring Committee
ILCOR	International Liaison Committee on Resuscitation
IQR	InterQuartile Range
LMA	Laryngeal Mask Airway
mHealth	Mobile Health
MHREC	Mulago Hospital Research and Ethics Committee
NEOSUPRA	NEOnatal SUPRupraglottic Airway
NICU	Neonatal Intensive Care Unit
PPV	Positive Pressure Ventilation
RA	Research Assistant
RCN	Research Council of Norway
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SDG	Sustainable Development Goal
SDG 3.2	Sustainable Development Goal number 3.2
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization

Definitions

Acidosis	increased acidity in the blood and other bodily tissues
Apgar	backronym for Appearance, Pulse, Grimace, Activity and Respiration
Apnoea	episodes when a neonate fails to make an effort to respire
Birth asphyxia	combination of the lack of oxygen and tissue-ischemia in the foetus or neonate caused by disruption of placental blood-flow, bleedings, uterine rupture, umbilical cord compression, infection or from a neonate failing to establish and maintain regular breathing at birth
Cardiotocography	parallel recording of the heart rate of the foetus in the uterus and uterine contractions
Early Neonatal Death	death within the first 7 days of life (WHO definition)
Early Neonatal Mortality Rate	death within the first 7 days of life per 1000 live births (WHO definition)
Endotracheal intubation	procedure involving intubation of the trachea
Electrocardiography	recording of the electrical activity of the heart
Extrauterine	outside the uterus
Foetus/foetal	the unborn offspring of an animal/human
Functional residual capacity	the volume of air present in the lungs at the end of passive expiration
Fresh stillbirths	intrauterine death of a foetus during labour or delivery
Gasping	the last respiratory pattern preceding terminal apnoea (also referred to as agonal breathing)
Gestational age	a measure of the age of the pregnancy in weeks taken from the first day of the last menstrual period
Grunting	sound during expiration created by the neonate breathing against a slightly closed glottis
Hypercapnia	a condition of abnormally elevated carbon dioxide (CO_2) levels in the blood
Hypoxia (cerebral)	oxygen deprivation (to the brain)
Innovation	creation, development and implementation of a new product, process or service, with the aim of improving efficiency, effectiveness or competitive advantage
Intrapartum	period from the onset of labour to birth
Intrauterine	inside the uterus
Ischemia	restriction in blood supply to tissue, causing a shortage of oxygen needed for cellular metabolism
Macerated stillbirths	intrauterine death of a foetus where it has started to decompose

mHealth	medical and public health practice, supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices (WHO definition)
Neonatal Mortality Rate	neonatal death during the first 28 days of life per 1000 live births (WHO definition)
Perinatal Mortality Rate	number of stillbirths and neonatal deaths from 28 completed weeks of gestation until the first 7 days of life per 1000 births (WHO definition)
Peak Inspiratory Pressure	the highest level of inflation pressure applied to the lungs during inspiration
Primary apnoea	asphyxiated neonates' initial response during positive pressure ventilation with an increased respiratory rate followed by apnoea, a drop in heart rate and increase in blood pressure. During this phase, most neonates will respond to stimulation and ventilation, with return of spontaneous respiration
Postpartum	period beginning immediately after birth
Positive pressure ventilation	delivery of air into the lungs by positive pressure
Respiratory function monitor	a monitor collecting information, such as airway pressures, flow and tidal volumes
Secondary apnoea	occurs when asphyxia continues after primary apnoea; a neonate responds with a period of gasping respiration, a drop in heart rate, and a fall in blood pressure. The neonate takes a last breath and then enters the secondary apnoea period. The neonate will not respond to stimulation alone, and death will occur unless resuscitation begins immediately. Immediately after birth, it is impossible to differentiate between primary and secondary apnoea
Stillbirth	a neonate dying at a late stage of pregnancy, before or during birth (WHO definition)
Strategy	an action aimed at achieving a desired goal in the future
Tidal volume	inhaled and exhaled volume of air during a breath
Very early neonatal death	death within the first 24 h of life (WHO definition)

Abstract

Background: Lack of oxygen at birth, birth asphyxia, accounts annually for around 700 000 deaths. Heart rate is important in evaluating a neonate and effective positive pressure ventilation (PPV) may prevent neonatal deaths. Evaluating heart rate by auscultation may be inaccurate and standard face-mask ventilation (FMV) may be inadequate. NeoTap Life Support (NeoTapLS) is a free-of-charge smartphone app for heart rate recording designed for low-resource settings. The laryngeal mask airway (LMA) is a tube used as an alternative to a face mask. Both of these innovations may be task-shifted to midwives who are on the front-line of neonatal resuscitation in low-resource settings. This thesis reports on investigations into whether these innovations and new strategies can potentially increase adherence to guidelines and thereby reduce neonatal mortality and morbidity.

Methods: Two observational studies and a clinical trial were conducted in Sweden and Uganda between 2014 and 2019. We investigated the accuracy and speed of heart rate assessment by NeoTapLS compared to a manikin, a metronome, pulse oximetry and electrocardiography, in simulations and in clinical use. A phase III open-label superiority randomized clinical trial, the *NeoSupra Trial*, compared LMA with face mask as a primary device for neonatal resuscitation carried out by midwives. The study involved neonates at ≥34 weeks of gestation and/or an expected birth weight of ≥2000 gram, thereby requiring PPV at birth. The primary outcome was a composite of 7-day mortality and moderate-to-severe hypoxic-ischemic encephalopathy, daily evaluated by Thompson scoring through Day 5.

Results: Simulation studies showed a high correlation between measured and true values. In the manikin study, 93.5% of the auscultations and 86.3% of the palpations differed by ≤5 beats, mean acquisition time 14.9 vs. 16.3 s. In the metronome study, 77% differed by ≤10. In clinical assessment by doctors of neonates not needing PPV 88% differed by ≤10 and by midwives in neonates needing PPV 48% differed by ≤10, median acquisition time 5 vs. 2.7 s. NeoTapLS showed very good sensitivity and specificity in detecting heart rate <100 bpm. The *NeoSupra Trial* had a complete follow-up data of 99.2%; the primary outcome occurred in 27.4% in the LMA arm and 24.4% in the FMV arm (adjusted relative risk, 1.16; 95% confidence interval 0.90 to 1.51; P=0.26). Seven-day mortality was 21.7% in LMA and 18.4% in FMV (adjusted relative risk 1.21; 95% confidence interval, 0.90 to 1.63). The proportion of moderate-to-severe HIE was 11.2 vs. 10.1% (adjusted relative risk, 1.27; 95% confidence interval, 0.84 to 1.93). Intervention-related adverse events were few and similar between the arms.

Conclusion: NeoTapLS is well adapted in the context it was used for swift and accurate heart rate recording by doctors. Clinical assessment by midwives was less accurate, suggesting that they may benefit from auscultation-focused training. LMA was safe in the hands of midwives but was not superior to a face mask in reducing early neonatal death and moderate-to-severe hypoxic-ischemic encephalopathy. It is suggested further investigations of these innovations and new strategies to explore the possibility of task-shifting its use to midwives in low-resource settings.

List of publications

Article I:
Myrnerts Höök S, Pejovic NJ, Marrone G, Tylleskär T, Alfvén T.
Accurate and fast neonatal heart rate assessment with a smartphone-based application – a manikin study.
Acta Paediatrica 2018;107:1548-1554.
Doi:10.1111/apa.14350.

Article II:
Myrnerts Höök S, Pejovic NJ, Cavallin F, Lubulwa C, Byamugisha J, Nankunda J, Tylleskär T, Alfvén T.
Smartphone app for neonatal heart rate assessment – an observational study.
BMJ Paediatrics Open 2020;0:e000688.
Doi:10.1136/bmjpo-2020-000688.

Article III:
Pejovic NJ*, **Myrnerts Höök S***, Byamugisha J, Alfvén T, Lubulwa C, Cavallin F, Nankunda J, Ersdal E, Blennow M, Trevisanuto D, Tylleskär T.
A randomized trial of laryngeal mask airway in neonatal resuscitation.
The New England Journal of Medicine 2020;383:2138-47.
Doi:10.1056/NEJMoa2005333.

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Thesis at a glance (article I-III)

Article I	
Aim	To determine the accuracy and speed of the NeoTap Life Support (NeoTapLS), a free-of-charge smartphone application that aims to assess a neonate's heart rate.
Participants	30 participants: eight doctors, six nurses, three nurse assistants, six nurse students, two medical students, three secretaries and two web designers.
Methods	This observational manikin study was carried out at Sachs' Children and Youth Hospital, Sweden. Participants used the NeoTapLS app to determine a randomly selected heart rate by auscultation and palpation using a Laerdal SimNewB manikin that simulates heart rates, defined as true values.
Results	1200 measurements were carried out. A high correlation was found between measured and true values by auscultation (Pearson´s correlation coefficient, 0.993) as well as by palpation (Pearson´s correlation coefficient, 0.986) with 93.5% of the auscultations and 86.3% of the palpations differing from the true value by five beats or fewer. The mean time to the first estimated heart rate was 14.9 seconds for auscultation and 16.3 seconds for palpation.
Conclusion	Heart rates could be accurately and rapidly assessed using the NeoTapLS app on a manikin.
Article II	
Aim	To evaluate the NeoTapLS app, which records heart rate with a screen-tapping method bypassing mental arithmetic calculations.
Participants	*Phase one* and *three*: 18 low-end users (midwives). *Phase two*: 2 high-end users (paediatric specialists).
Methods	This observational study was carried out in Uganda in three phases. In *phase one*, a metronome rate (n=180) was recorded by low-end users using NeoTapLS. In *phase two*, heart rate (n=69) in neonates not needing positive pressure ventilation (PPV) was recorded by high-end users using NeoTapLS versus pulse oximetry. In *phase three*, heart rate (n=235) in neonates needing PPV was recorded by low-end users using NeoTapLS versus electrocardiography (ECG).
Results	In high-end users, the mean difference was 3 beats per minute (bpm) higher with NeoTapLS versus pulse oximetry in neonates not needing PPV (95% agreement limits, −14 to 19 bpm), with median acquisition time of 5 seconds. In low-end users, the mean difference was 6 bpm lower with NeoTapLS versus metronome (95% agreement limits, −26 to 14 bpm) and 3 bpm higher with NeoTapLS versus ECG in neonates needing PPV (95% agreement limits, −48 to 53 bpm), with median acquisition time of 2.7 seconds. The agreement between NeoTapLS and ECG was good in heart rate categories of 60–99 bpm and ≥100 bpm (kappa index 0.71, 95% confidence interval, 0.63 to 0.79). Heart rate <60 bpm had few measurements.
Conclusion	Heart rate could be accurately and rapidly assessed by high-end users using a smartphone application in neonates not needing PPV in a low-resource setting. Clinical assessment by low-end users in neonates needing PPV was less accurate with wider confidence interval but adds clinically important information.

Article III	
Aim	To investigate if ventilation with a cuffless laryngeal mask airway (LMA) over face mask has potential advantages on mortality and morbidity during neonatal resuscitation in asphyxiated neonates in a low-resource setting.
Participants	1163 participants, neonates needing PPV with gestational age $\geq$34 and birth weight $\geq$2000 gram (566 LMA, 597 face mask)
Methods	This phase III open-label superiority randomized controlled clinical trial in Uganda compared the use of an LMA versus face mask in neonatal resuscitations performed by midwives. The primary outcome was a composite of 7-day mortality and moderate-to-severe hypoxic-ischemic encephalopathy through Day 5.
Results	The follow-up rate was 99.2%. The primary outcome occurred in 154/563 (27.4%) neonates in LMA and 144/591 (24.4%) in face mask arms (adjusted relative risk, 1.16; 95% confidence interval, 0.90 to 1.51; P=0.26). Seven-day mortality was 21.7% in LMA and 18.4% in face mask arms (adjusted relative risk, 1.21; 95% confidence interval, 0.90 to 1.63). The proportion of moderate-to-severe hypoxic-ischemic encephalopathy was 11.2% in LMA and 10.1% in face mask arms (adjusted relative risk, 1.27; 95% confidence interval, 0.84 to 1.93). Rates and main analysis were based on complete cases; findings were materially unchanged in the sensitivity analysis. The frequency of pre-defined intervention-related adverse events was low and similar between the arms.
Conclusion	In asphyxiated neonates needing PPV, LMA was safe in the hands of midwives but was not superior to face mask in reducing early neonatal death and moderate-to-severe hypoxic-ischemic encephalopathy.

Table of Contents

1 Introduction

This thesis discusses how best to support non-breathing neonates immediately after birth in low-resource settings using innovations and new strategies. The thesis will be focused on heart rate (HR) assessment using a smartphone app, and airway access for ventilatory support with the use of a laryngeal mask airway (LMA), following its effect on adherence to international neonatal resuscitation guidelines and effect on neonatal mortality and morbidity. To understand why some neonates need assistance at birth, I will first introduce the physiological transition occurring in neonates during a normal birth and what can go wrong.

1.1 Happy Birthday

In the majority of births, the neonate does not need advanced intervention to start breathing. There is a wide range of what is referred to as a 'normal' birth, and the experience is different both for mothers and neonates. A 'normal' birth could be described as a spontaneous start of labour between 37-42 weeks of pregnancy and the birth of a neonate breathing within the first 30 s of life.[1,2] It could also include immediate skin-to-skin contact after delivery and breastfeeding within the first hour of birth. However, even in a 'normal' delivery the neonate undergoes a dramatic transition from intrauterine (within the uterus) to extrauterine (outside the uterus) life.

1.2 Transition to extrauterine life

The transition from intrauterine to extrauterine life for the foetus, is a chain of physiological events in both circulation and respiration that are not fully understood to this day. The transition is driven by a number of events.[3-6] Before birth the foetus is supported by the placenta, for example for oxygenation (Figure 1a). After birth, the neonate is oxygenated by gas exchange in his/her own lungs (Figure 1b).

The ductus arteriosus is a vascular foetal structure connecting the proximal descending aorta to the roof of the main pulmonary artery. In normal cases, the ductus arteriosus closes after birth and becomes the ligamentum arteriosum. This is

due to a shift of blood-flow from the placenta to the pulmonary vessels, resulting in a left-to-right flow through the ductus arteriosus, which leads to ductal closure.

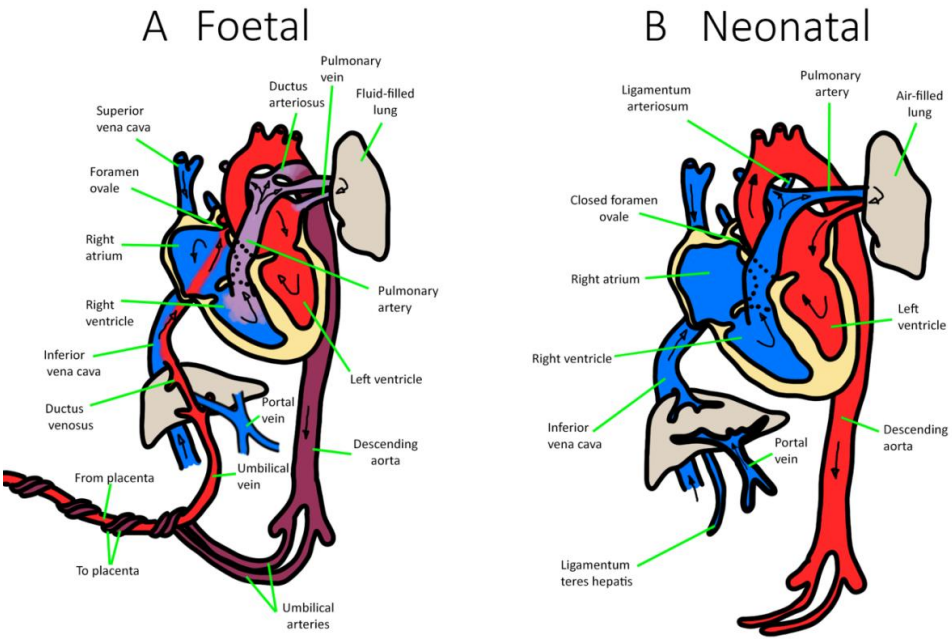

Figure 1. a) Foetal and b) neonatal circulation. From Textbook of Neonatal Resuscitation, 7th ed., 2016. Adapted by Abbe Höök and published with the kind permission of the American Academy of Pediatrics.

Foetal breathing movements starts in the 11th week of gestation. On the day of birth, pressure in the birth canal, changes in temperature and changes in circulation have been considered factors triggering the start of breathing. At birth the fluid-filled non-inflated lungs with high resistance become filled with air during the first breath. The lungs should remain filled with air, creating a space for air even after exhalation, called the functional residual capacity. The mean oxygen saturation during intrauterine life is ~58%[7] and may drop to as low as 30% during labour.[8] Median peripheral capillary oxygen saturation after birth reaches 68% at 1 min, 92% at 5 min and 97% at 10 min in term neonates.[9] Neonates normally clear their airways of fluid within 2-5 breaths, and the cardiac output from the right ventricle is shifted towards the lungs (Figure 1).[10]

A study of rabbits showed that air/liquid only moved toward the distal airways during inspiration, indicating that pulmonary pressures plays an important role in airway liquid clearance at birth.[11] Breathing efforts in healthy neonates and ventilation in non-breathing neonates affecting the HR have been investigated in recent years; they show that HR increase spontaneously in the first min after birth in breathing neonates with a minimal effect of cord clamping, and a consistent positive relationship between delivered volumes and HR increase from <100 beats per min (bpm) to a stable HR ~160 bpm after 2-3 min.[12-14]

1.3 Birth asphyxia

The need for interventions at birth are common, with ~10% of neonates requiring some assistance at birth.[2,15,16] Many of these neonates start breathing after tactile stimulation, which refers to warming, drying the skin and rubbing the back or the soles of the feet of the neonates, measures recommended in the guidelines to stimulate breathing.[17-20] How it acts is unclear, but experimental studies have validated a positive effect.[21,22] However, a recent retrospective video-analysis of preterm neonates showed that only in a small proportion had an effect that could be observed on video.[23]

Birth asphyxia is the lack of oxygen in combination with tissue-ischemia, which may cause brain injury and death. Birth asphyxia, nowadays, often referred to as intrapartum (i.e. during childbirth) related events, accounts for ~23% of neonatal mortality, leading to ~700 000 deaths/year.[24-26] Asphyxia can occur prior to the birth due for instance to placental blood-flow disruption, bleeding, uterine rupture, umbilical cord compression and infection. At birth, asphyxia is caused by failure to establish and maintain regular breathing due to respiratory or cardiovascular impairment, such as insufficient breathing efforts, secretion plugs or cardiac abnormalities, leading to hypoxia, hypercapnia and respiratory or metabolic acidosis. But a combination of intrapartum and postpartum asphyxia is common.

Hypoxia due to birth asphyxia should be differentiated from other causes of brain injury, such as congenital metabolic diseases.[27] Intrapartum related events can be identified by monitoring abnormalities in foetal HR, thereby indicating a possible

need for resuscitation efforts, and can be associated with fresh stillbirth (intrauterine death of a foetus during labour) and early neonatal deaths (death within the first 7 days of life).[28-30] Observation of postpartum events will be discussed later.

In a high-resource setting, with a strong and well-equipped healthcare system, doctors and nurses on call 24/7 use advanced interventions to give every neonate a chance of survival. In low-resource settings, there is often a lack of health personnel, training, equipment and medicines, leading to inadequate or absence of the appropriate interventions.

Hypoxic-ischemic encephalopathy (HIE) is brain injury caused by hypoxia-ischemia; it is a serious health problem that often leads to long-lasting neurological consequences, such as neurodevelopmental disabilities - seizure disorder, cerebral palsy and learning disability.[31] An estimated 3-5 per 1000 live term-births are affected.[32] In low-resource settings, the incidence may be 10-fold higher.[33] Cooling criteria have been used as a criterion for initiating brain protection by therapeutic hypothermia treatment in high-resource settings.[34] These are, for example, an Apgar score of 5 or less at 10 min, ongoing resuscitation at 10 min, metabolic or mixed acidosis within the first hour of life. Studies, including 3 systematic reviews, report that therapeutic hypothermia is a way to treat HIE, and have been shown to be effective in reducing death and disability. It is safe to use in intensive care in high-resource settings.[35-39] Treatment should be started as soon as possible but within 6 hours (h) after birth; the target core temperature is 33.5 ± 1°C, with the treatment lasting for ~72 h.[40,41]

A systematic review and metanalyses on all published randomised or quasi-randomised controlled trials of therapeutic hypothermia in low-and middle-income countries was published in 2013.[42] They concluded that it was not associated with a statistically significant reduction in neonatal mortality, although the confidence intervals were wide and not compatible with results seen in high-income countries. They suggested part of this may be due to a sicker population and suboptimal care at the neonatal intensive care units (NICUs). There is a lack of adequately run clinical trials on cooling in low-resource settings.[43] Existing methods of therapeutic

hypothermia are expensive and difficult to translate into practise in low-resource settings due to, for example, the inability to cool during transport, and often the long distances to NICUs that have an adequate power supply and the right equipment. New inventions are under investigation.[44]

1.4 Neonatal mortality

Neonatal mortality, defined as deaths within 28 days of life, has decreased by 51% from 1990 to 2018, i.e. from ~5.0 to ~2.5 million, currently accounting for 47% of all under-5 deaths worldwide.[45] This is, of course, a great success, but neonatal mortality varies widely globally, and most of sub-Saharan Africa, the Eastern Mediterranean and South Asia are lagging behind (Figure 2). Nevertheless, today ~1 million neonates die on the first day of life and further 2 million within 6 days.[45] Stillbirths accounts for ~2.6 million deaths per year, half of which occur after the onset of labour.[46]

It is clinically difficult to distinguish fresh stillbirths and intrauterine death of a foetus during labour or delivery from neonates suffering from severe birth asphyxia.[46,47] This probably influences the estimated global perinatal mortality rate.

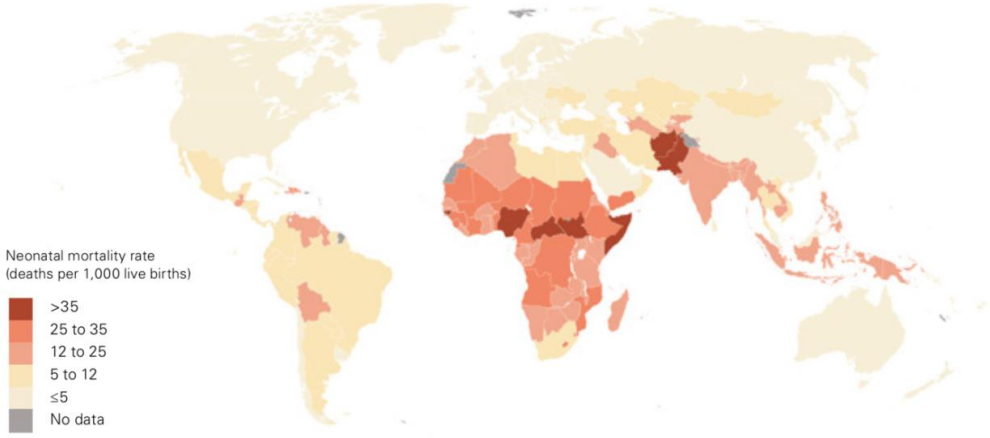

Figure 2. Neonatal mortality rate (deaths per 1000 live births) by country, 2018. Levels & Trends in Child Mortality Report 2019. Estimates developed by the UN Inter-agency Group for Child Mortality Estimation Note: The classification is based on unrounded numbers. Published with the kind permission of UNICEF.

To reach the Sustainable Development Goal number 3 target 3.2 (SDG 3.2) in each country reporting a neonatal mortality rate of ≤12 per 1000 births by 2030,[48] improvement in neonatal resuscitation is crucial.[49-51] About 60 countries have to accelerate their efforts to reach the target.[24,52,53] Many efforts have been made, such as the global Every Newborn Action Plan launched in 2014, which provided a road-map of strategic actions for ending preventable neonatal mortality and stillbirth, thereby contributing to reducing maternal mortality and morbidity.[54] The plan was based on evidence published in *The Lancet* Every Newborn series.[26] In a constantly developing world, translation into practice of new evidence-based tools, innovations and new strategies must focus on reaching the most vulnerable people in the world, i.e. neonates in low-resource settings.[55]

1.5 Neonatal resuscitation

For neonates that are not breathing, state-of-the-art resuscitation is of utmost importance for a healthy survival.[51] Most studies report that 3-6% of neonates do not respond to stimulation alone, which means that approximately 6 million neonates a year need resuscitation at birth.[2,15,16] Advanced resuscitation (i.e. chest compressions, intubation, or medications) is required for <1% of all neonates.[16] Positive pressure ventilation (PPV) is the delivery of air into the lungs. If PPV is not administrated or is ineffective, birth asphyxia may develop or be aggravated.[56] Deprivation of oxygen affects the organs, such as the heart, reducing its beating with the result that less blood reaches the brain, potentially causing injury.

A normal foetal HR is considered to be 120-160 bpm, based on expert consensus. Neonates needing PPV are considered to suffer from either primary or secondary apnoea, the two initially possibly looking alike. In primary apnoea, the neonate typically has a HR >60 bpm, and may respond to stimulation or ventilation relatively quickly by starting to breathe.[57,58] A neonate in secondary apnoea typically has a HR <60 bpm, and stimulation is insufficient; the neonate may respond with occasional irregular breaths (gasping), decrease in HR and falling blood pressure if PPV is not immediately given (Figure 3).

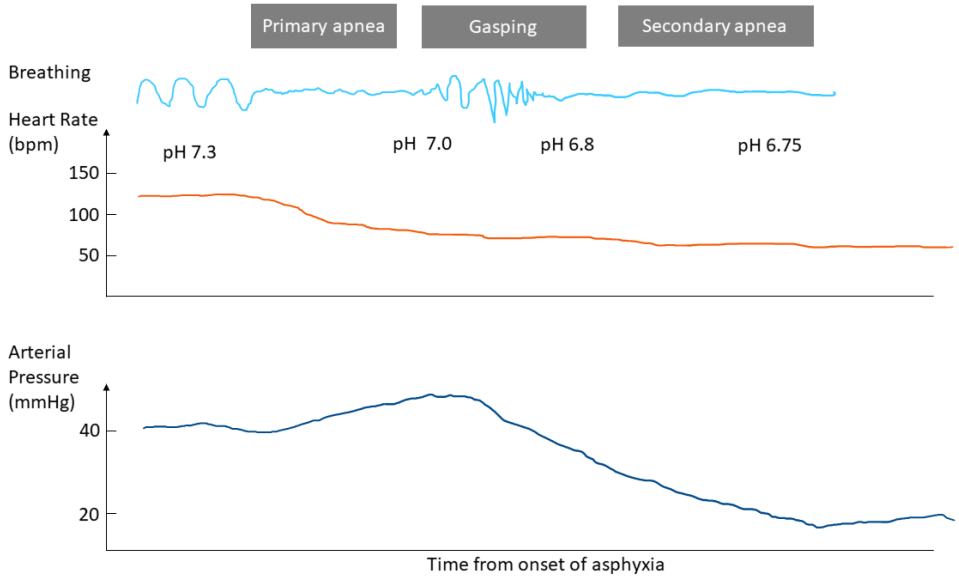

Figure 3. Physiological changes associated with primary and secondary apnoea in the neonate. Adapted by N. Pejovic from Kattwinkel Neonatal Resuscitation Textbook, 5th Edition, 2006, with the kind permission of N. Pejovic.

1.5.1 The International Liaison Committee on Resuscitation (ILCOR)

Neonatal resuscitation is an emergency intervention and all health personnel involved in the delivery or care of neonates should be prepared to provide immediate resuscitation of neonates needing PPV. All health personnel are called to follow internationally accepted guidelines for best practice. The International Liaison Committee on Resuscitation (ILCOR) was formed in 1992 in collaboration with major resuscitation organisations worldwide. ILCOR released its first treatment recommendations for neonatal resuscitation in 2000, based on the latest available evidence. It has since issued updated recommendations every fifth year, focusing on resuscitation practices in high-resource settings (Figure 4).[17,18,20] The ILCOR 2015 Consensus on Sciences with Treatment Recommendations (CoSTR) was considered when planning the studies for this thesis. How proper HR assessment should be performed and PPV should be given in low-resource settings, where training and adequate equipment may be lacking, has yet to be defined by ILCOR.

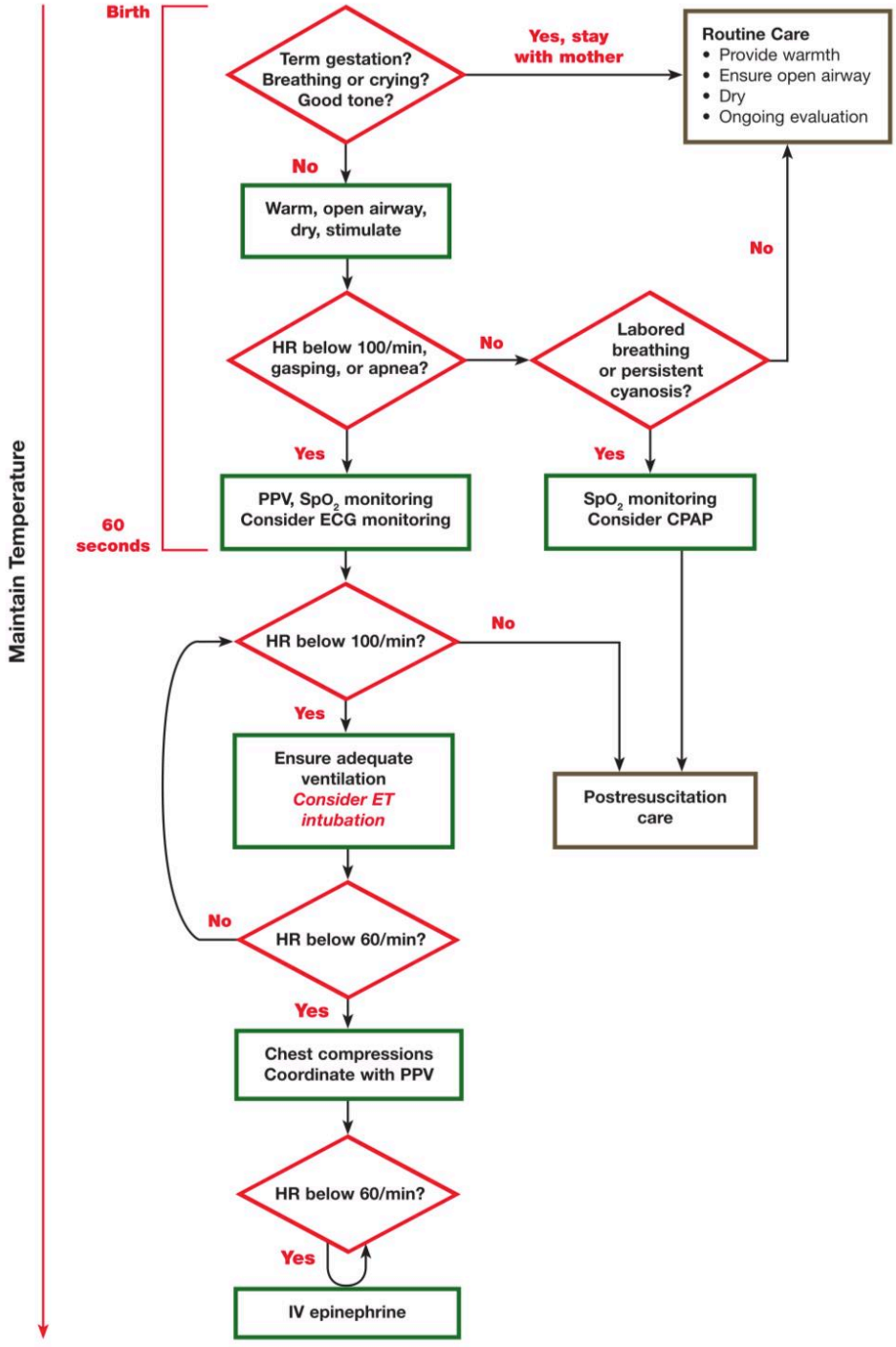

Figure 4. The 2015 ILCOR action plan for neonatal resuscitation. Published with the kind permission of Elsevier.

1.5.2 Helping Babies Breathe (HBB)

International guidelines have historically focused on resuscitation in high-resource settings. Low-resource settings, where most of the neonatal deaths occur, have been lacking appropriate training material for health personnel and appropriate equipment suited in this context. The World Health Organization (WHO) took the lead in creating a basic neonatal resuscitation curriculum, publishing in 1998 the first guideline targeting low-resource settings.[59] The American Academy of Pediatrics and partners followed, which developed Helping Babies Breathe (HBB), recently updated in a 2nd edition (Figure 5).[60-62] HBB is based on the ILCOR guidelines with a focus on prompt PPV in non-breathing neonates. They have produced a set of instructions and tools for easy teaching and training: a color-coded action plan, flip charts, workbooks, a mannequin and other equipment.[63,64] The concept of The Golden Minute© teaches first assessments and care of neonates and informs that PPV should start within 1 min after birth in neonates requiring it. After implementing HBB in 8 hospitals in Tanzania in 2009, a 47% reduction in early neonatal death and a 24% reduction in fresh stillbirths were reported; HBB introduction in India reduced intrapartum stillbirth rate by 46%.[65,66] However, another study in Tanzania reported a better performance in simulated neonatal care and resuscitation 7 months after one day of HBB training, but the improvement did not transfer to clinical practice.[67] Since the rollout of the HBB program in 2010, workshops have taken place in >80 countries and a network of master trainers has been instructed.[68] The HBB action plan does not teach advanced resuscitation (e.g., chest compressions), interventions that could be relevant to referral hospitals in low-resource settings.[15] HBB is now included in Helping Babies Survive (HBS) evidence-based, hands-on training programs developed to reduce neonatal mortality in low-resource settings.[69] HBS began with the HBB neonatal resuscitation techniques, but now also includes the programs 'Essential Care for Every Baby', 'Essential Care for Small Babies' and 'Improving Care of Mothers and Babies: A guide for improvement teams'.

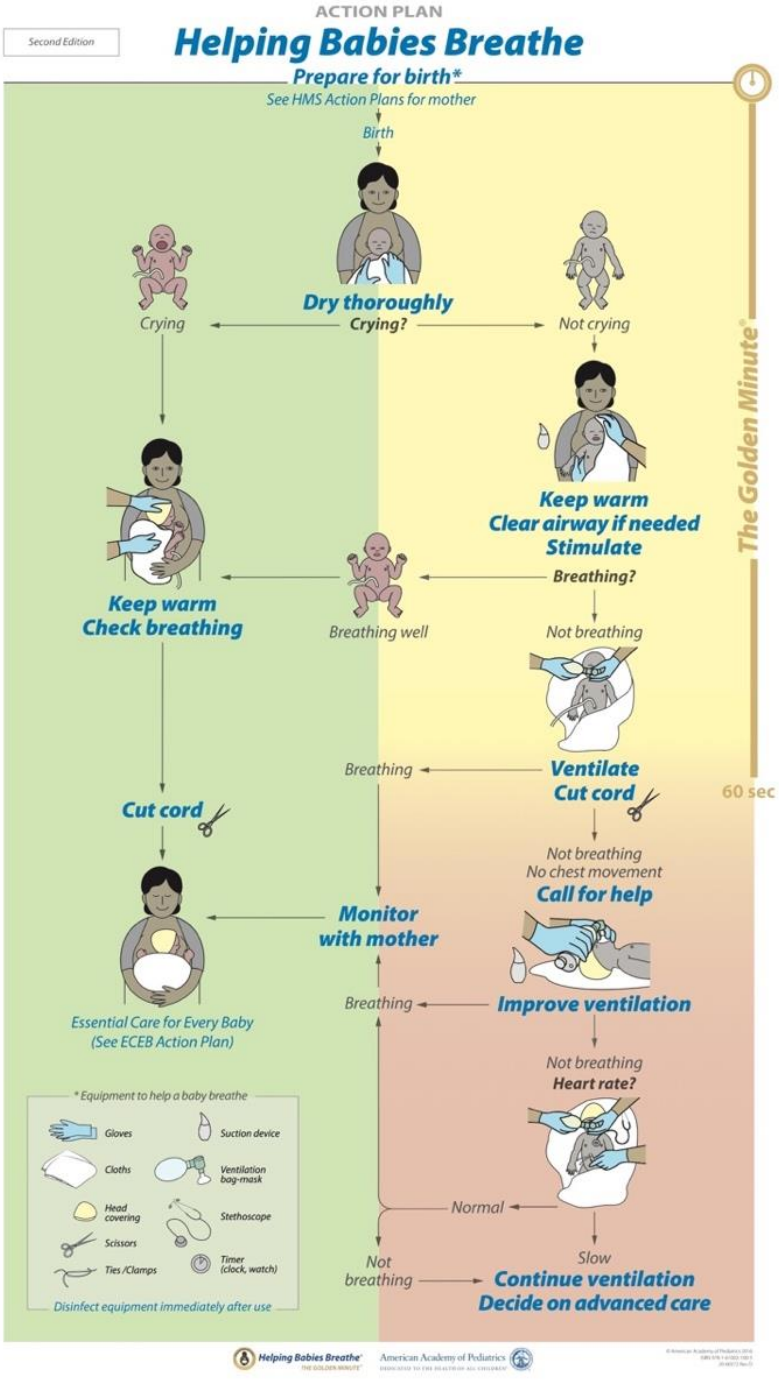

Figure 5. Helping Babies Breathe (HBB) action plan, 2nd edition. Published with the kind permission of the American Academy of Pediatrics.

1.6 Assessment of neonates

The assessment of neonates immediately after birth is the cornerstone of neonatal resuscitation, in which time is an extremely important factor. Primary assessment is both visual and physical. The colour, tonus and breathing efforts of the neonate are essential, as are the assessment of HR guiding resuscitation efforts.

1.6.1 Apgar

In high-resource settings, the analysis of cord blood may indicate the severity of birth asphyxia. In low-resource settings, blood tests are normally unavailable and health personnel will base their assessment of the severity of asphyxia on ventilation time and the Apgar score. This score was invented by Virginia Apgar in the 1950s as a method of clinically evaluating neonates, being used in both high- and low-resource settings.[70-73] Five variables are scored 0-2 each: HR, breathing, skin colour, muscle tone and reflex irritability, giving a maximum score of 10. It is assessed at 1 and 5 min, but at 10 min or more was added at a later stage, called the *expanded* Apgar score.[72] Apgar gives an indication of the state of the neonate, but does not reveal the aetiology or prognosis.[74] A low Apgar score (<7) at 5 min is associated with higher risk of HIE.[75-77]

1.6.2 Heart rate (HR)

HR is one of the most important clinical parameters used to evaluate a neonate, to guide the management and predict the outcome.[19,78,79] HR reflects the state of the foetus or neonate both during and after birth and indicates whether the foetus/neonate is suffering hypoxia. The most common way for physicians to measure HR in a neonate is by auscultation. This is a 3-step procedure; first, auscultating the heart, second interpreting what is heard (first and second heart sounds), and third translating it by a number by an algorithm. The HR value of neonates is conventionally classified into 3 categories: <60 bpm very low; 60–99 bpm low and 100 bpm or above normal HR. Apnoea (no breaths), gasping (irregular breaths) and an HR <100 bpm are the threshold indicators for starting PPV, and a HR <60 bpm despite effective ventilation is the threshold for starting chest compressions.

Guidelines suggest HR assessment and start of PPV within 60 seconds (s) for neonates needing PPV.[17,20] Evaluation of HR by auscultation and palpation has been proven to be imprecise, even when assessed by doctors in high-resource settings.[80-84] However, doctors HR assessment by auscultation compared to pulse oximetry and electrocardiography (ECG) has recently been shown to be quick and reasonably accurate in neonates not needing PPV.[85] Studies during neonatal resuscitation with less experienced health personnel are lacking. Neither pulse oximetry nor ECG is fast enough to enable delivery room personnel to follow international resuscitation guidelines of HR within 60 s after birth, and HR by auscultation and palpation is inaccurate.[86-90] Nevertheless, HR determination by physical examination is recommended if pulse oximetry and/or ECG are unavailable.[17,19,91] ECG remains the gold standard to continuously monitor a neonate´s HR immediately after birth, meaning that, according to most reviews, this is the best available way to monitor HR.[89,92] ECG is faster in giving the first HR value compared to pulse oximetry,[93,94] but both are relatively expensive and rarely available in low-resource settings. ECG can also be difficult to apply due to wet skin and hence it becomes time-consuming.[95] Pulse oximetry is sensitive to excessive motion and low blood perfusion, making it slow and often unreliable in the delivery room. One study reported a median of 68 s needed to obtain a HR.[95] In an observational study, the mean time interval from attaching the pulse oximeter on the neonate to the first displayed HR was 84 s.[96]

The HBB action plan (Figure 5) includes assessment of HR, and the training kit includes a plastic stethoscope. However, the training program does not include any specific auscultation-focused training; non-doctoral health personnel in low-resource settings rarely have sufficient training or access to a personal stethoscope.[15] The assessments of HR by non-doctoral health personnel are prone to be incorrect and may lead to inadequate interventions and adverse outcomes.[97]

1.6.3 Breathing/respiratory rate

Assessing the breathing effort in the neonate is done by a visual check of chest-rise and by auscultation. The breathing should be regular with a rate of 30-60 per min. Grunting is an expiratory sound made by a neonate breathing against a slightly closed glottis. It is common as the neonate's way of creating a pressure and keep air in the lungs, ensuring they do not collapse and remain open. Gasping are irregular breaths at ~12 per min and may be misinterpreted as breathing.[98] It can be a sign of hypoxia and/or decreased perfusion of the brain, as well as being a possible indicator of cardiac arrest. Neonates showing this behaviour should be promptly resuscitated.[99] Any irregular breathing must be further investigated.

1.6.4 Assessment of hypoxic-ischemic encephalopathy (HIE)

HIE is a leading cause of neonatal mortality and morbidity that affects at least one million neonates each year.[100] Neonates can compensate for brief periods of oxygen depletion, but if the hypoxic event is too long, brain tissue will start to be damaged. Data from Uganda showed that asphyxiated neonates had signs of major recent brain injury using early cerebral ultrasound imaging, suggesting prolonged or severe acute exposure to hypoxia.[101,102] Death and neurodevelopmental disability were common and early clinical parameters predicted impairment outcomes. The current understanding of longer-term childhood outcomes of asphyxia in low-resource settings remains limited.

The Thompson score is a clinical tool to assess the severity of HIE of a neonate in the first days of life following birth asphyxia. The score has a high sensitivity and specificity predicting HIE and adverse outcomes (death or severe disability).[103,104]
The Thompson score is based on daily assessments of 9 neurological parameters of neonates born with birth asphyxia (Table 1), with a maximum score of 22.

In normothermic neonates, a maximum score of >10 any day during the first 7 days of life predicts an abnormal outcome with 100% sensitivity and 61% specificity.[103]
A Thompson score of ≥7 predicts an abnormal 6-h amplitude-integrated electroencephalogram (aEEG; sensitivity 100%, specificity 67%) and is consistent

with cooling criteria.[105] A 2-year follow-up of HIE survivors with a Thompson score of 6-10 reported abnormal outcome in 20.6% of the patients.[101] More recently a statistically significant correlation between mortality and morbidity and day 1 Thompson score was reported.[104]

The decision to use Thompson scoring in our trial was based on the fact that previous studies at the study site in Uganda had used this method.[101,102,106]

Table 1. The Thompson score assessing 9 neurological parameters. The maximum score is 22.

Sign	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
Level of consciousness	Normal	Hyperalert/stare	Lethargic	Comatose
Fits	None	<3 per day	>2 per day	-
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	-
Grasp	Normal	Poor	Absent	-
Suck	Normal	Poor	Absent± bites	-
Respiration	Normal	Hyperventilation	Brief apnoea	Apnoea
Fontanel	Normal	Full, not tense	Tense	-

2 Innovations and new strategies

Innovation is the creation, development and implementation of a new product, process or service, with the aim of improving efficiency, effectiveness or competitive advantage. A strategy is an action aimed at achieving a desired goal in the future. A pubmed search in 2013 for medical devices addressing the health of neonates in low-resource settings, reported few innovations or new strategies for neonates in peer-reviewed medical journals.[107] Most devices were infant warmers, neonatal resuscitators, and phototherapy devices. In 2015, the same group made a systematic review which showed that most neonatal health devices being reported were in fact iterations of already existing interventions, not innovations, and were only modified for a new context equal to new strategies.[108] Rigorous randomized trials focusing on outcomes were rare. It was concluded that there was a need to assess the impact of innovations on health outcomes and provide evidence on the potential for scale-up, feasibility and acceptability.

Making innovations and new strategies available to health personnel in low-resource settings at the time and place of birth is essential. There is not only a need for new devices and strategies, but also a great challenge to translate evidence-based knowledge into practise, the so-called 'know-do gap'.[109] The environment for midwives in low-resource settings is challenging for the translation of knowledge into practise. A Cochrane review in 2017 looked at factors influencing the provision of intrapartum and postpartum care by skilled birth attendants in low- and middle-income countries.[55] The ability of midwives to provide quality care was limited by a) lack of training both in their pre-service and in-service education, b) lack of equipment, and c) not the least, time. Access to training and supervision, well-equipped, well-organised healthcare facilities would save lives and take us closer to the SDG 3.2 goal.

2.1 Mobile health and smartphone apps

While a standardized definition of mobile health (mHealth) has not yet been established, the WHO uses the following definition: "mHealth or mobile health is

medical and public health practice, supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices. mHealth involves the use and capitalization on a mobile phone's core utility of voice and short message service, as well as more complex functions, including general packet radio service, third and fourth generation mobile telecommunications, global positioning systems and Bluetooth technology".[110]

Mobile health can be used to support health-related tasks, such as monitoring, data collection, education and consultation. This strategy is increasingly used in low-resource settings where mHealth can extend the reach of health services and is becoming a formal part of healthcare. The number of mobile phone users is expanding quickly and was expected to pass 4.68 billion in 2019.[111] The widespread use of mobile phones highlights the significant opportunities to have a global impact on health behaviour, and midwives are encouraged to be involved in the mHealth revolution.[112] To include midwives in the development of relevant and functional apps is essential to get apps suitable for the clinical context in low-resource settings. A significant proportion of health personnel in low-resource settings have their own smartphone, the number increasing, giving us the idea of using a tool that the health workers already have.[111,113]

2.2 Development of NeoTapLS (Life Support)

Tap4Life is a registered non-profit organization based in Stockholm, Sweden (reg. no. 802495-5216) started by members of our research team. The project started as part of a research project in Uganda involving Makerere University (Uganda), The Centre for International Health (Norway) and the Karolinska Institutet (Sweden).[114] The lack of reliable monitoring equipment for neonates in the delivery room lead to the development of the first prototype for point-of-care HR registration by Michael Vaganov, a software engineer from California, and was further developed with a grant from Innovationsfonden, Region Stockholm, in 2014. With further funding Tap4Life has continued this development with constant feed-back from users both during the observational studies and the trial presented in this thesis.

The mission of Tap4Life is to improve healthcare by the development of mHealth applications, freely downloadable on Google-play and App-store. The Tap4Life team is at present focusing on neonatal mortality and morbidity in low- and middle-resource settings and doing research on their products to assess their quality and feasibility in clinical use. NeoTapLS (Life Support) produced by Tap4Life (Figure 6)[115] is based on a screen-tapping method, no probes needing to be attached to the neonate. The interface is designed to be visible even if a latex glove protects the phone. Health personnel even in remote areas will be able to use their phone as a tool that may improve performance in the immediate care of neonates.

Figure 6. a) Tap to record the neonate's heart rate by the NeoTapLS application. Heart rate <100 bpm (yellow) at 37 s: prepare for ventilation.
b) Heart rate <60 bpm (red) at 2 min and 11 s: start chest compressions? c) Heart rate ≥100 bpm (green) at 3 min and 37 s: neonatal resuscitation is going well. Published with the kind permission of Tap4Life.

A major feature of NeoTapLS is the algorithm-based screen-tapping assessment of HR. The user auscultates the heart sounds or feel the pulse and taps the beat on the screen a minimum of 3 times from which the app generates a number. The NeoTapLS calculates the HR based on the user's last 3 taps on the smartphone screen and bypasses the need for any mental arithmetic. This algorithm can also be used to

monitor foetal HR. An instructional video on '*How to use NeoTapLS'* is available on YouTube.

The features of NeoTapLS have evolved over the years after feedback from users and video analysis on how it is used. The present version of NeoTapLS, used in article II, has the following features:

- Pop-up messengers on important aspects of neonatal resuscitation
- Prepare for birth – checklist for tools important for neonatal resuscitation
- Oral and written messages for guidance through the resuscitation
- Colour-coded foetal HR
- HR and Breathing Rate registration within 10-15 s after birth, colour-coded according to HBB guidelines
- Resuscitation timer
- Automated Apgar score calculation
- NeoPacer – pacing the recommended ventilation pace by sound, visual feedback and vibration
- Tracking of vital events
- Identification of danger signs
- Referral decision support
- Tutorials on the cornerstones of neonatal resuscitation:
    - prepare for birth
    - the art of resuscitation
    - stimulation
    - suction
    - ventilation and more

NeoTapLS is now freely available on Google Play and App Store. A free-of-charge iPad version, NeoTapAS (Advanced Support), for high-resource settings is also freely available. Both apps have the tapping function for HR.

2.3 Respiratory support worldwide

International guidelines on neonatal resuscitation are currently unanimous that PPV should be initiated within 60 s after birth in neonates requiring PPV.[17,19,91] This gives the carer limited time to determine the state of the neonate by physical examination, including measurement of HR. Prompt initiation of PPV is critical to the outcome. In 2012 it was shown that an increased risk of prolonged hospitalization and death occurs of 16% for every 30 s delay in initiating PPV using face-mask ventilation (FMV).[2] The United Nations Commission on Life-Saving Commodities for Women and Children in 2012 started with the goal of increasing access to life-saving medicines and health supplies for people living in low-resource settings. They produced a list and indicated efforts needed to increase access to 13 essential commodities, including neonatal resuscitation equipment (mask, valve and bag).[116]

2.3.1 The bag of air

Mouth-to-mouth resuscitation has been used since biblical times as a technique using one's own lungs as a reservoir of air to breath into the mouth of the non-breathing neonate.[117] In some settings, mouth-to-mask resuscitation remains in use. Most settings today use devices for the same purpose. To have good equipment is essential in minimizing the risk of mask leakage, excessive pressures and volumes causing pneumothorax (collapsed lungs). A self-inflatable bag is the most common way to provide PPV and create functional residual capacity in low-resource settings. Bags can be for both single and multiple use. New inventions, such as the Upright Resuscitator (Laerdal, Stavanger, Norway), have been introduced recently, and good quality bags are sold at a low price.[116,118,119] The reusable, high quality NeoNatalie Resuscitator (Laerdal, Stavanger, Norway; Figure 7) is most often administrated with the HBB kit, and has also been used in studies included in this thesis. The size of the lungs differs with the size of the neonate, which must be remembered, especially when delivering PPV to preterm neonates. Tidal volume - the normal inhaled and exhaled volume of air- of preterm and term neonates ranges from 6.5 to7 ml per kg, and a tidal volume from 4 to 8 ml per kg is recommended during resuscitation with 40-60 breaths per min.[17,19,91,120] A bag size for neonates of <5 kg is recommended to

be 200-320 ml and a typical bag size is 220-240 ml. Increasing the squeezing gives higher pressures.

Figure 7. NeoNatalie Resuscitator including 2 face masks. Published with the kind permission of Laerdal Global Health.

2.3.2 Face-mask ventilation (FMV)

FMV can be a lifesaving intervention; it is a proven technique and may in emergencies be as effective as endotracheal intubation (placing a tube in the windpipe), if administered properly. It has been estimated that FMV could reduce intrapartum related death by 40%.[121] However, it is a difficult task, with mask leakage and poor chest movements being reported.[122-124] The most common round mask with a soft rim must create a good seal, and the bag must be of the right size and undamaged. Difficulties in achieving proper FMV may be due to upper airway obstruction.[125] Clearing the airway, repositioning the mask, opening the mouth or increasing the pressure may resolve these problems, but in the case of failure one needs to consider an alternative airway as an endotracheal tube (ETT) or a laryngeal mask airway (LMA).

2.3.3 Endotracheal tube (ETT)

During cardiopulmonary resuscitation, FMV is normally the first choice for administrating air into the lungs, followed by ETT if neonatal depression continues.[126] ETT insertion is difficult and requires a laryngoscope and a trained doctor; it is often impossible to perform in low-resource settings.[127] Improper management can cause damage to the neonate, such as laryngospasm and subglottic trauma, and may cause cardiopulmonary failure.[16]

2.3.4 Laryngeal mask airway (LMA)

The LMA was designed and also produced by Archie Brain, who published the first article in 1981.[128] The aim was to produce an airway device more effective than the FM and less invasive than the ETT, without the need for a laryngoscope and with minimal instrumentation of the larynx.[126] LMA causes fewer side effects than ETT in paediatric surgical procedures.[129] LMAs are used in anaesthesiology during surgical procedures both for adult and children. It is also used in pre-hospital resuscitations by paramedics because it is easy to use. LMAs are today also referred to as 'laryngeal mask' or 'supraglottic device', and as the LMA in this thesis. ILCOR 2015 states that an LMA during neonatal resuscitation may be considered as an alternative to FM for neonates weighing >2000 grams or delivered around or after 34 weeks of gestation.[17,18,20] The LMA can be used with a standard self-inflatable bag or a T-piece resuscitator. The cuffed LMA (Figure 8) has a pre-curved cuff and is placed blindly along the palate of the neonate until it stops at the top of the oesophagus, creating a seal. After placement, the cuff is inflated according to size of the neonate. In the Democratic Republic of Congo, training in inserting a cuffed LMA on manikins with midwives and physicians was highly successful in a short time.[130] Newer, more user-friendly, devices have been developed that do not need to be cuffed (Figure 8d). Previous studies showed that the LMA facilitated effective PPV, but currently there is limited evidence of its use; the use of LMA in neonatal resuscitation needs further investigation.[131] LMAs ease of use shows it is suited for non-doctoral health personnel in low-resource settings.

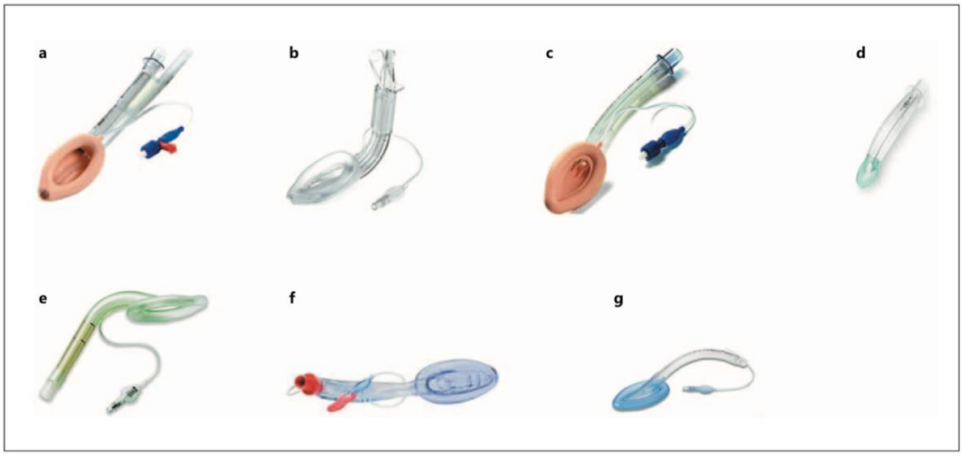

Figure 8. a) LMA Classic™ b) LMA Supreme™ c) LMA ProSeal™ d) i-gel® e) Ambu®AuraOnce™ f) Air-Q. g) Shiley™. Published with the kind permission of Karger publishers.

2.3.5 Uncuffed LMA: The i-gel®

The i-gel LMA (Intersurgical Ltd, Wokingham, Berkshire, UK; Figure 8d) was introduced in 2007 and is now widely used for surgery requiring general anaesthesia. This cuffless, latex-free, single-use LMA has an interface made of a soft gel-like transparent thermoplastic elastomer. The material produces a light pressure on the pharyngolaryngeal structure, producing a good seal without the cuff (Figures 9 and 10).[132] I-gel is easy to place because of its small size and precurved shape; one study showed reduction of the insertion time from 18 to 13 s compared to a cuffed LMA.[133]

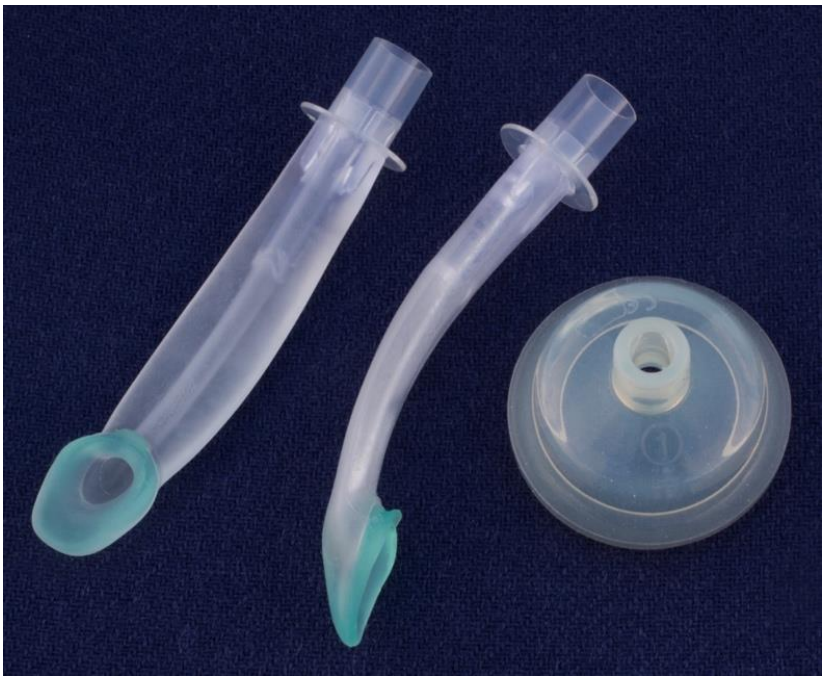

Figure 9. The i-gel from 2 angles and the Laerdal face mask. Photo: T. Tylleskär.

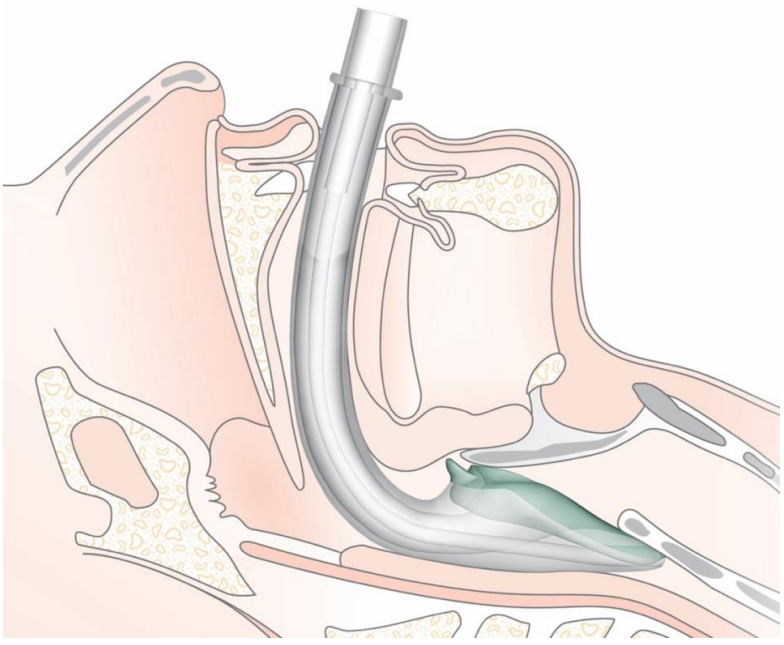

Figure 10. Anatomical transect showing the position of the i-gel. Published with the kind permission of Intersurgical.

2.4 Prior research

Previous manikin studies with LMA showed that a brief training on a manikin gave a 100% success rate, and the LMA was well received by non-doctor users even in low-resource settings.[134-136] In 2016, our team compared the performance of health personnel in Uganda when using an LMA or a FM on a manikin.[137] The study again reported a 100% success rate on first insertion with the LMA. FM was significantly less effective in achieving effective PPV, and the failure rate at the first attempt was 28%. This drew us to the conclusion that LMA would be more effective than FM in establishing PPV.

In 2014-15, we conducted a phase II trial on the safety of i-gel in the hands of midwives in Uganda, ClinicalTrials.gov Identifier: NCT02042118. Neonates needing PPV were randomized to either i-gel LMA or FM. This prospective, observational study on 49 neonates (24 in the LMA and 25 in the FM arm) had a success ratio of 100% for the insertion of i-gel.[114] The study showed no adverse events (AEs), shorter ventilation time, quicker pick-up of HR and fewer admissions to the NICU in the LMA arm (Table 2). In short, these are very encouraging results.

Table 2. Overview of results from our phase II trial in Uganda 2014-15.[114]

	Laryngeal Mask Airway N=24	Face Mask N=25	P Value
Ventilation time in seconds mean(±SD)	93 (52)	140 (90)	p=0.02
Heart rate at 90 seconds (±SD)	148 (39)	127 (45)	p=0.07
Heart rate at 120 seconds (±SD)	161 (33)	134 (49)	p=0.01
Heart rate at 180 seconds (±SD)	167 (26)	143 (36)	p=0.01
Assistance from supervising physician	3	6	p=0.46
Admission to the neonatal unit	5	8	p=0.52
Hypoxic ischemic encephalopathy	0	2	p=0.49
Adverse events related to ventilation	0	0	
Deaths at 24 hours	0	0	

2.5 Rationale

As discussed above, innovations and new strategies have the potential to improve the outcome of neonatal resuscitation; reaching the SDG 3.2 now needs our full attention. Targeting low-resource settings with the highest mortality rates and implementation of evidence-based interventions could prevent many early neonatal deaths and decrease morbidity in surviving neonates.

HR assessment is a very important clinical parameter in neonatal resuscitation and is often performed nowadays by midwives in low-resource settings. They still lack training and equipment, creating a barrier to optimal performance. Research on HR assessment during neonatal resuscitation, including midwives in low-resource settings, has not yet been carried out, which could improve outcomes. The need to develop a low-cost, rapid and accurate alternative to HR monitoring during neonatal resuscitation has been emphasised.[89,92]

Neonatal resuscitation with uncuffed LMA has been investigated by our team, but the benefit in terms of mortality and morbidity remains unknown.[114,137] Our studies indicate a beneficial effect in the short-term and the ease-of-use of the LMA in the context of neonatal resuscitation in low-resource settings. Before this thesis, no large studies designed to assess mortality and morbidity had been carried out. PPV is the single most important component of successful neonatal resuscitation.[17,19,91,119] Effective PPV has the potential to reduce by 40% intrapartum-related deaths.[65,138-141] The effectiveness and safety of LMAs compared to FM as the primary device for neonatal resuscitation have still to be fully assessed. Task-shifting the use of LMAs to non-doctors could be one way of improving the outcome.

3 Aim and objectives

The overall aim of this thesis has been to explore whether innovations and new strategies could improve neonatal resuscitation practices, and thereby reduce mortality and morbidity in a low-resource setting.

The specific objectives were:

I. To determine if health personnel could randomly determine selected simulated heart rates on a Laerdal SimNewB manikin by auscultation or palpation, using the NeoTapLS (Life Support) application (article I)

II. To assess the NeoTapLS app in 3 phases (article II):
    a. In *phase one,* a metronome rate recorded by low-end users (midwives)
    b. In *phase two*, heart rate in neonates not needing positive pressure ventilation recorded by high-end users (paediatricians) using NeoTapLS versus pulse oximetry
    c. In *phase three*, heart rate in neonates needing positive pressure ventilation recorded by low-end users using NeoTapLS versus electrocardiography

III. To assess in a phase III open-label superiority randomized controlled clinical trial the effectiveness and safety of the laryngeal mask airway versus face-mask ventilation in neonatal resuscitation in reducing early neonatal death and moderate-to-severe hypoxic-ischemic encephalopathy (article III)

4 Subjects and methods

This thesis consists of 2 observational studies (articles I and II) and one clinical trial (article III). The observational studies include both simulations and clinical assessments on neonates. The setup of the phase III trial, the Neonatal Supraglottic Airway Trial (*NeoSupra Trial)* was used to collect data for article II, *phase three*. Phase III refers to a study that tests the safety and how well a new treatment works compared with a standard treatment. In most cases, treatments move into phase III clinical trials only after they meet the goals of a phase II clinical trials. A phase II trial has been performed prior to the *NeoSupra Trial*.[114] Phase II and III in this thesis should be differentiated from *phase two* and *phase three* (article II).

4.1 Article I and II - assessing NeoTap Life Support (NeoTapLS)

Article I and II assessed the NeoTapLS application. The hypothesis was that NeoTapLS was faster than pulse oximetry and ECG, and accurate enough to follow neonatal guidelines. The findings could be important for low-resource settings where pulse oximetry and ECG are rarely available. Providing NeoTapLS in a low-resource setting inexpensively support HR assessment, but it also needs to be feasible to use in environments where most neonatal resuscitations are done by non-doctoral health personnel.

4.2 Article III, the *NeoSupra Trial*

The hypothesis in the *NeoSupra Trial* was that effective PPV would be easier to achieve with an LMA than with a FM, with the potential of decreasing early neonatal death and moderate-to-severe HIE. The findings could be important for low-resource settings where the majority of intrapartum-related events occur. Providing LMA in a low-resource setting is expensive; it can only be justified if there is a substantial gain in using the LMA over the standard of care FM. Based on our prior phase II trial, we estimated that early neonatal death and moderate-to-severe HIE could be reduced by 25%, a difference large enough to have policy implications.[114,142] The trial protocol followed the SPIRIT guidelines and has been published.[142]

4.3 Study settings

Article I was conducted at Sachs´ Children and Youth Hospital, Stockholm South General Hospital, Stockholm, Sweden (Figure 11). The hospital has the largest emergency care unit in the Nordic region. The paediatric emergency unit provides care services to neonates, children and young adults up to 18 years of age. The hospital operates one of the largest maternity clinics in Sweden, providing excellent opportunities for clinical research (Table 3).

Figure 11. Sachs´ Children and Youth Hospital, Stockholm South General Hospital, Stockholm, Sweden. Published with the kind permission of Södersjukhuset AB.

Article II and III were conducted in Uganda at the High-risk Labour Ward and Operating Theatre, Department of Obstetrics and Gynaecology, Mulago National Referral Hospital, Kawempe, Kampala, connected to the Makerere University (Figure 12).[114] The hospital also serves as a general hospital for Kampala, a fast-growing area. The Kampala city population was 62 000 in 1948 and had grown to 1.5 million inhabitants by 2014, with the Kampala metropolitan area having ~4.5 million (Table 3).[143] The Kawempe division opened in 2016 and the hospital changed its name in 2019 to Kawempe National Referral Hospital. It is currently home to the Directorate of Obstetrics and Gynaecology and the NICU. In 2018 the Kawempe division had ~25 000 deliveries and ~60% were referred to the hospital from other health facilities due to complicating factors.

Figure 12. Mulago National Referral Hospital, Kawempe division, Kampala, Uganda. Photo: T. Tylleskär.

The University of Bergen and Karolinska Institutet have long-lasting academic collaborations with Makerere University, and have conducted a number of studies within the field of neonatal resuscitation and HIE reporting and classification (Figure 13).[101,102,106,114,137,144] These studies report a high rate of HIE after intrauterine insults and birth asphyxia, as well as the need to improve HBB training.[145]

Uganda has a high rate of neonatal mortality. From 2000 to 2006 there was a small decrease (from 33 to 27 deaths per 1000 live births), but since then it has remained unchanged.[146] Neonatal mortality, as in the rest of the world, has come to constitute a larger proportion of neonatal and under-5 years mortality.

Figure 13. Mulago National Referral Hospital also housing College of Health Sciences of Makerere University. Photo: T. Tylleskär.

Table 3. Information about the 2 hospitals involved in article I-III

	Location	City population and hospital coverage	Academic collaboration	Visits
Article I	Sachs' Children and Youth Hospital, Stockholm, Stockholm South General Hospital, Stockholm, Sweden	1.5 million inhabitants in Stockholm 2015. The hospital serves 500 000 inhabitants	Clinical research and teaching connected to Karolinska Institutet and international collaborators	Emergency units has 17 600 children/year Maternity unit has 7000 deliveries/year
Article II and III	High-risk Labour Ward and Operating Theatre, Department of Obstetrics and Gynaecology, Mulago National Referral Hospital, Kampala, Uganda	1.5 million inhabitants in Kampala 2014. The hospital serves the Kampala metropolitan area with 4.5 million inhabitants	Clinical research and teaching connected to Makerere University and international collaborators	In 2015: 29 000 antenatal visits 39 000 deliveries 11 000 postnatal visits 15-30 caesarean sections/day

Recruitment for the trial (article III) was done from 2 resuscitation tables in the operating theatres and one resuscitation area in the delivery suite, all without warmers. Around 150-200 midwives and doctors participated in the obstetric care at the hospital and took part in the study. Research assistants (RA) and a supervisor were present 24/7 at the resuscitation area. The health personnel had clinical experience of ventilating neonates with a FM and were introduced to the LMA as part

of the trial.[114] Suction bulbs and self-inflating bags with masks (Laerdal, Stavanger, Norway) were always available. ETT was rarely carried out due to lack of skills and adequate equipment. Intravenous fluids were delivered through peripheral intravenous lines on rare occasions. Embrace Nest™ (Phoenix Medical Systems, India) infant warmer for transport of neonates and pulse oximetry for monitoring were available on site but were mostly out of order. The setup of equipment was equal to our previous trial at the study site, but with new suction devices (Penguin Suction Device, Laerdal, Stavanger, Norway) for easier cleaning. New standardized cleaning processes of equipment were introduced, done by RAs on a daily basis.

At the time of the trial, the capabilities/available services of the Mulago National Referral Hospital NICU were as follows:

- Free flow oxygen, CPAP, and self-inflating bags and masks for resuscitation. There were no ventilators
- Pulse oximeters were available, but not enough for monitoring all sick neonates in need. Health personnel had to identify neonates to put on continuous monitoring and others had intermittent checks of their oxygen saturation
- Availability of parenteral fluids were as follows: dextrose, Ringer's lactate, normal saline. No total parenteral nutrition
- The anticonvulsants available were: intravenous phenobarbitone, used as the first line according to the national guidelines, and phenytoin as second line
- Antibiotics in use were: ampicillin, gentamicin, cefotaxime and ceftriaxone
- Blood tests available were: complete blood counts, serum electrolytes, liver function, renal function, blood grouping and cross-matching
- Not available: aEEG monitoring or therapeutic hypothermia
- There was no space for continuous Kangaroo Mother Care, which was done intermittently when neonates were admitted

4.4 Participants

Article I

With the aim of covering a wide range of existing or non-existing clinical skills, the participants were recruited from a variety of professional and educational backgrounds. None of them had previous experience in the NeoTapLS app and all those we approached agreed to take part in the study. We disregarded prior experience in smartphone management (Table 4).

Article II

In *phase one* and *three* we involved low-end users (midwives). In *phase two* we involved high-end users (paediatric specialists) (Table 4 and Figure 14). These were sub-studies of our previous trial on LMA versus FM[114] and the *NeoSupra Trial* (article III).

Figure 14. Setup for article II phase two. Photo: T. Tylleskär.

Article III

The inclusion criteria of this trial were as follows: neonates born in the hospital, with parental consent, estimated gestational age ≥34 weeks and/or estimated birth weight ≥2000 gram, requiring PPV at birth. Neonates with major malformations and stillbirths did not fulfil the inclusion criteria (Table 4).

Table 4. Design and participants

	Design	Participants	Recruitment
Article I	Observational simulation manikin study, testing the NeoTapLS app using a Laerdal SimNewB manikin that simulate heart rates	30 participants: 8 doctors, 6 nurses, 3 nurse assistants, 6 nurse students, 2 medical students, 3 secretaries and 2 web designers.	Springtime 2014 Centre for Education in Paediatric Simulation Stockholm, Sweden
Article II	Prospective observational study in 3 phases assessing rates and heart rates with the NeoTapLS app *Phase one:* NeoTapLS compared to a metronome *Phase two:* NeoTapLS compared to pulse oximetry *Phase three:* NeoTapLS compared to ECG	*Phase one* and *three*: 18 low-end users (midwives) *Phase two*: Two high-end users (paediatric specialists)	May, 2015, to January, 2019. High-risk Labour Ward and Operating Theatre Kampala, Uganda
Article III	Phase III open-label superiority randomized controlled clinical trial to compare the use by midwives of a laryngeal mask airway with face-mask ventilation	1163 asphyxiated neonates	May 8, 2018, to August 12, 2019. High-risk Labour Ward and Operating Theatre Kampala, Uganda

4.5 Equipment and data recording

4.5.1 NeoTap Life Support (NeoTapLS)

In articles I and II, we investigated the use of NeoTapLS. During neonatal resuscitation HR gives feed-back on the effect of resuscitation efforts, as well-functioning ventilation raises the HR in almost all asphyxiated neonates. It is critical to be able to measure HR in both foetuses and neonates. However, HR assessment is not easy and studies show that the evaluation often is inaccurate.[81,82,84,88,89,92,95,147-150]

A significant proportion of health personnel in low-resource settings have their own smartphone.[111,113] RAs and study doctors of the *NeoSupra Trial* received phones preloaded with a beta software version of NeoTapLS during the data collection of article II *phase one* and *three*. This allowed us to get feedback on the interface and the design of the app.

In article II *phase three,* the use of NeoTapLS allowed intermittent assessment of the HR during resuscitation with the output being visible on video recordings.

4.5.2 SimNewB®

The SimNewB (Laerdal, Stavanger, Norway) manikin used in article I is an advanced manikin designed to help improve neonatal resuscitation (Figure 15). It generates both breathing and simulated HRs, providing realistic training. An extensive ECG Library in the computer attached to the manikin can produce cardiac-, umbilical- and brachial- simulated HRs from 10 to 300 bpm.

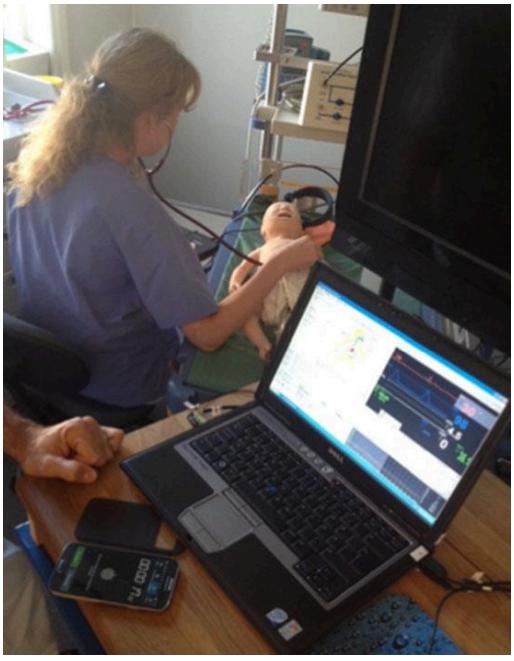

Figure 15. Participant auscultating the precordium of the manikin and at the same time tapping the screen of the smartphone with the NeoTapLS application. Photo: S. Myrnerts Höök, the participant agreed to this publication.

4.5.3 NeoNatalie™ and Newborn Anne™

We used 2 training manikins in training for the *NeoSupra Trial*. NeoNatalie (Laerdal, Stavanger, Norway) is an inflatable manikin included in the HBB training kit (Figure 16a). It has been developed to provide the needs in teaching the initial steps of resuscitation. The operator can manually simulate breathing movements and HRs on the manikin. The Newborn Anne™ (Laerdal, Stavanger, Norway) neonatal baby simulator has been used in training LMA insertion (Figure 16b). It is designed for training in neonatal airway management, including the use of positive-pressure airway devices, and the placement of LMA and ETT.

a b

Figure 16. a) Face-mask ventilation training with NeoNatalie™ according to the Helping Babies Breathe 2nd edition. Photo: S. Myrnerts Höök.
b) Insertion of LMA training with Newborn Anne™. Photo: N. Pejovic.

4.5.4 Metronome

In article II *phase one,* a metronome app (Metronome; Beijing Buluobang Co, Ltd.) was used to generate audible metronome rhythms. It is the world´s most famous free-of-charge metronome app generating exact rhythms. Random rates generated for the participants, selected using a number generator sets over the range of 20–150 bpm.[151]

4.5.5 Pulse oximetry

In article II *phase two,* pulse oximetry (PalmSAT 2500, Nonin Medical, Plymouth, USA) was used as the true value since no other monitoring equipment was available at the time (Figure 17). It is a small, handheld pulse oximeter designed to accurately assess peripheral capillary oxygen saturation and pulse rate.

Figure 17. Two heart rate assessment methods in use. The first generation NeoTapLS (background left), showing a heart rate of 174 bpm and pulse oximetry (PalmSAT 2500, Nonin Medical, Plymouth, USA, background right), showing a heart rate of 176 bpm. Photo: T. Tylleskär, with the kind permission of the parents.

4.5.6 Electrocardiography (ECG)

In article II *phase three,* the first 49 data collected from NeoTapLS were compared to traditional ECG (Philips Intellivue X2, Amsterdam, The Netherlands), a combined multi-measurement module and transport monitor (Figure 18). The ECG was put on a neonates directly on arrival to the resuscitation table.

4.5.7 Dry-electrode Electrocardiography (ECG)

In article II *phase three,* the last 186 data collected from NeoTapLS were compared to dry-electrode electrocardiography, NeoBeat Newborn HR Meter (Laerdal, Stavanger, Norway; Figure 18). It is a reusable and easy-to-use HR meter providing continuous display of neonatal HR. NeoBeat was put on a neonate's abdomen on arrival at the resuscitation table and displayed the HR within s. NeoBeat uses dry electrodes to pick up an ECG-based signal, making it comparable to conventional ECG.

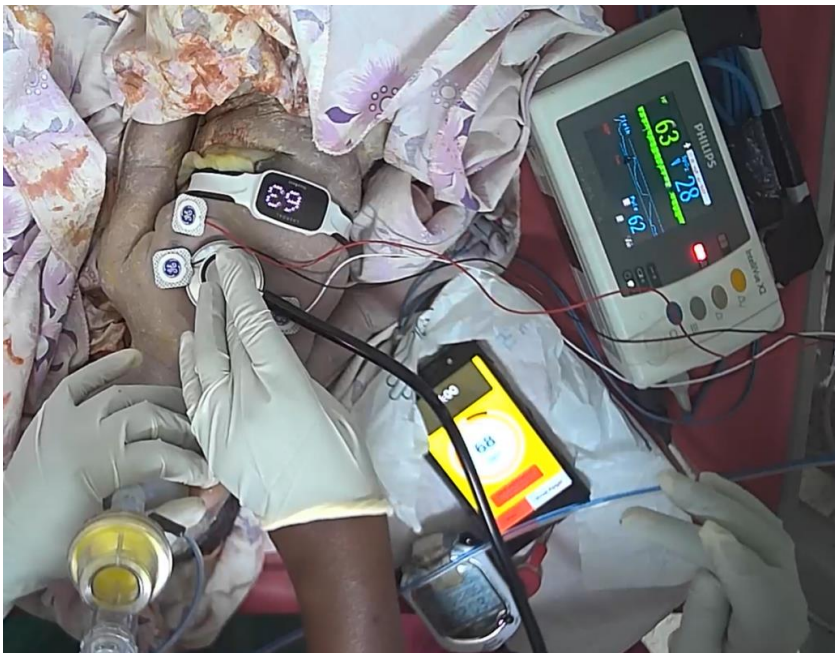

Figure 18. NeoBeat dry-electrode electrocardiography (left), showing a heart rate of 63 bpm, conventional ECG with a heart rate of 63 bpm (right, in green numbers), and NeoTapLS (middle) with a heart rate of 68 bpm. Photo: S. Myrnerts Höök, with the kind permission of the parents.

4.5.8 Video monitor

In the *NeoSupra Trial* (Article III), we video-recorded all resuscitations with a HD 1080P Black box AI-IP018 camera (Shenzen Aishine Electronics Co. Ltd, China) attached above each of the 3 resuscitation tables (Figure 19). The same setup had been used for data collection for Article II *phase three.* The view of the camera was adjusted to show only the neonate and the hands of the health personnel. The cameras were small and well disguised, and our impression was that the health personnel forgot about the cameras within days, and thus it did not affect their performance.

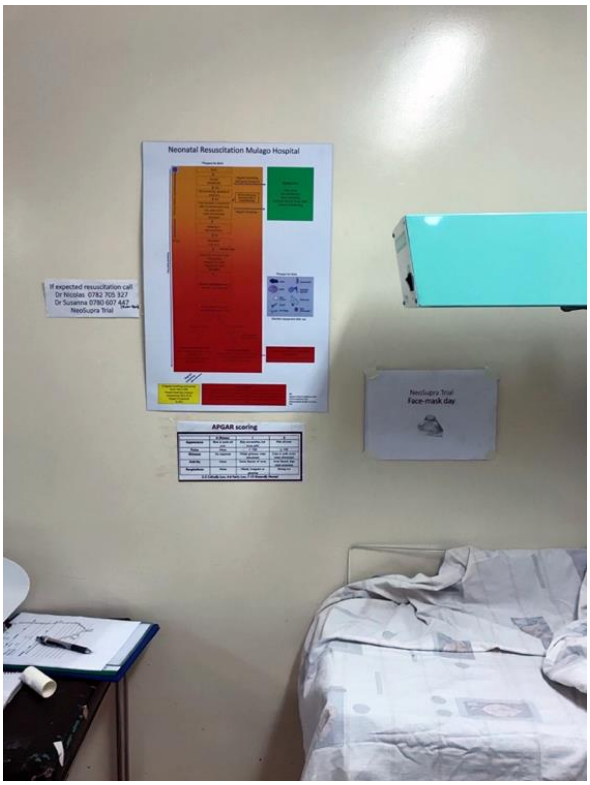

Figure 19. Setup at one of the resuscitation tables with the Mulago Hospital Resuscitation Flow Chart (Annex II), Apgar scoring reminder and note showing randomization of the day on the wall. The camera is hidden behind the warmer above the table. Photo: S. Myrnerts Höök.

4.6 Training

Article I

The participants, disregarding previous knowledge of NeoTapLS or smartphones, were introduced to the setup of the NeoTapLS and the Laerdal SimNewB simulation manikin for 3-5 min. The patient simulator was used for all simulations and is capable of generating heart tones as well as umbilical and brachial pulsations. The instructions were to determine the simulated HR by auscultation of the precordium or palpation of the brachial pulse of the manikin, and simultaneously tap the pace they heard or felt on the screen of a smartphone a minimum of 3 times, with the NeoTapLS app installed. They were also instructed to say 'stop' when they had generated a number they were relying on.

Article II

The midwives in article II *phase one* and *three* were trained within the framework of the *NeoSupra Trial,* as explained below. The midwives, disregarding previous knowledge of NeoTapLS or smartphones, were introduced to the NeoTapLS app for 3-5 min. The instructions in *phase one* were to determine the rate of a metronome by listening to the sound and simultaneously tap the pace they heard on the screen of a smartphone a minimum of 3 times, with the NeoTapLS app installed. They did not receive any further training before the data collection in *phase three*. The paediatric specialists in *phase two* were well familiar with NeoTapLS and had used it prior to the study. They did not receive further training before data collection started.

Article III

A one-day extended and modified HBB course (2nd edition) were held involving all midwives regularly exposed to performing neonatal resuscitation (~150 persons).[68] This training included FMV practice and a module for use of LMA in a manikin (SimNewB). From 20 to 25 participants and 4-5 facilitators (2 paediatricians and local HBB instructors) participated in each session (Figure 20). We used 7 NeoNatalie inflatable manikins and 2 SimNewB manikins. Two NewLifebox-R (Advanced Life Diagnostics, Weener, Germany) neonatal respiratory function monitors were used to optimize training in ventilation, giving objective feed-back on respiratory rate, airway leakage (%), peak inspiratory pressure (cm H_2O) and tidal volumes (ml per kg). Three successful LMA insertions combined with adequate chest-rise in the manikins were required of each participant. Suction practice was de-emphasized. HBB 2nd edition courses to new providers and refresher courses were held throughout the trial.

Doctors involved in daily Thompson scoring of neonates at the NICU, who had already received and practiced the scoring system in a previous study,[106] were given a refresher course prior to start of recruitment. The severity of asphyxia was based on the Thompson score used to assess signs of HIE.[103,105]

Figure 20. Midwives certified after the modified HBB 2nd edition course, including the use of LMA. Photo: S. Myrnerts Höök; the participants agreed to the publication of the photo.

4.7 Randomization

Article III

Recruitment for the *NeoSupra Trial* continued around the clock from May 8, 2018, to August 12, 2019, with a short interruption of a few weeks during May-June 2019. The resuscitations were carried out on 3 resuscitation tables at different locations in the hospital and could coincide with each other. Because of the nature and emergency of neonatal resuscitation, it was not feasible to randomize every birth potentially requiring resuscitation of the neonate. To manage this challenging setup, we chose day-by-day cluster randomization with the help of an independent statistician, using randomly selected block sizes of 4 to 8. The block sizes were determined by the number of arms, meaning that block size had to be divisible by the number of treatment arm, in this case 2. In this trial, block sizes of 4, 6 and 8 were randomly selected. This block randomization method is designed to generate equal sample sizes

in the different arms, at the same time making it difficult to anticipate the next randomization arm.

All neonates enrolled each day (defined as 08:00 am to 8:00 am the following day) were randomized for the same treatment. The randomization was concealed in sealed and dated envelopes. A new envelope was opened each morning at 8.00 am by an RA who also checked the 3 resuscitation tables, adjusted the signs and changed to the device for the day at the tables (Figure 21). The device not assigned for the day was available in a sealed box next to the resuscitation table, if needed to improve ventilation. The instruction was to continue ventilation for 3 min with the device of the day and, if chest rise was inadequate, to reposition the LMA or reapply the FM before considering switching. When switching occurred, a report had to be filled in explaining the reason. The decision to allow a switching of device in the trial was based on ILCOR recommendations.[17,18,20]

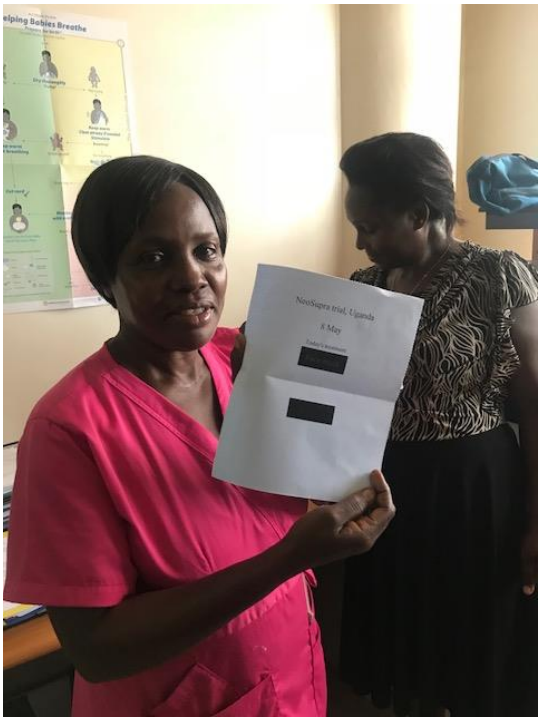

Figure 21. Opening of the first concealed envelop of NeoSupra Trial 8th in May 2018. Photo: S. Myrnerts Höök; the research assistant agreed to the publication of the photo.

4.8 Data collection and management

Article I

In this manikin study, data were collected and managed by me referred to hereafter as the researcher. I was a residential doctor in paediatrics at the time. Before starting a scenario, the manikin was programmed with a randomly generated simulated HR and had no active respiration.[151] The researcher told the participant to start measuring the rate and simultaneously started a stopwatch. When the participant had generated a number thought to be right, they said 'stop'. The researcher stopped the stopwatch and asked the participant for the number displayed on the NeoTapLS screen. Acquisition time, defined as the time from start to stop, and the number on the NeoTapLS screen were noted for all scenarios. The data were transferred to an Excel file at the end of the day.

Article II

In this prospective observational study in 3 phases, data were collected and managed by the researcher, a paediatric specialist at the time.

In *phase one*, rates were randomly selected using a number generator set in the range of 20–150 bpm,[151] and presented by a metronome, masked to the participants. The rates were presented for ~20 s. The participants recorded the rate with the NeoTapLS and wrote down the number on separate papers collected by the researcher at the end of each session, and the data were again transferred to an Excel file.

In *phase two*, pulse oximetry was placed on the neonate on arrival at the resuscitation table by one high-end user (a neonatologist) and HR was assessed using NeoTapLS by the second high-end user (the researcher) as soon as the HR was displayed on the pulse oximeter. Directly after HR was assessed using NeoTapLS, the second high-end user checked the HR on the pulse oximeter (unmasked) and noted both HRs. Acquisition time of NeoTapLS was noted (defined as s from start to end of tapping). Data were collected on-site when high-end users were available, before being transferred to an Excel file.

In *phase three*, ECG was placed on the neonate by the researcher or an RA when feasible directly after arrival at the resuscitation table. HR was assessed by low-end users (midwives) using NeoTapLS once HR had been displayed by ECG and compared with HR obtained simultaneously by ECG (not masked to the participants). The midwives continued to monitor HR with the NeoTapLS as many times as they thought appropriate for the clinical situation. All paired HRs (HR by NeoTapLS at the same time as HR by ECG) until end of resuscitation were collected. The acquisition time of NeoTapLS was noted. The first 49 HR data were supervised by the researcher and collected on-site by conventional ECG (Philips Intellivue X2, Amsterdam, The Netherlands), the data being recorded for transfer to an Excel file at the end of the day. The following 186 HR data were unsupervised and collected from video review compared with dry-electrode ECG (NeoBeat) and entered directly into an Excel file. Data were collected each day from the camera memory card and transferred to 2 separate hard drives. Data on Apgar and weight were collected from the Case Report Forms (CRF) of the *NeoSupra Trial* (Annex I) and double-entered using Android devices running the Open Data Kit V.2.0 tool suite.[152]

Article III

In this phase III open-label superiority randomized controlled clinical trial, the *NeoSupra Trial,* data were collected and managed by a team. This team consisted of one trial manager, 3 investigators, 3 doctors at the NICU, 18 RAs and 2 data entry managers. RAs were on site for 24/7, recording with a stopwatch time from birth to arrival at the resuscitation table. At arrival the neonates were filmed, and the data could be retrieved by video review. However, observations during resuscitation were timed by the RAs with a stopwatch in case of video failure. Data was collected each morning from the 3 camera memory cards and transferred to 2 separate hard-drives. Ventilation time was double-checked by video review each morning. Videos could also show if the neonate was in fact breathing and there was no need for PPV, in which case the information was excluded. Assistance by supervising physician, advanced interventions, e.g. CPR, and any switch to an alternative device could also be reviewed on videos.

Data from mothers and neonates were collected bedside from clinical charts and interviews on day 0 by the RAs and filled into pre-coded CRF 1 and 2 (Table 5 and Annex I). The CRFs were reviewed daily by the local trial manager for quality control. Weekly meetings were held with the RAs to discuss the data and correct deviations from the Standard Operational Procedure. Doctors at the NICU assessed neonates on their Thompson score on days 1-5 and filled a daily CRF 3 (Annex I).[103] CRF 4 was filled by research NICU doctors, RAs or the local trial manager on day 7 or above (Annex I). Data were double entered into Open Data Kit (ODK, https://opendatakit.org) by the 2 data entry managers from the paper CRFs and transferred to an encrypted server. Data-cleaning was managed by the researcher, and data were also corrected after review of videos and scanned CRFs. The clean data-set was transferred to R software version 3.5 (R Foundation for Statistical Computing, Vienna, Austria)[153] for final analysis.

Table 5. Timeline of the participants in the NeoSupra Trial.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Prior consent	X							
Deferred consent		X						
Randomisation	X							
Monitoring of resuscitation	X							
Video recording	X							
Id-bracelet infant and mother	X							
Filling CRF part 1	X							
Filling CRF part 2	X							
Thompson score (if admitted)	(X)	(X)	(X)	(X)	(X)	(X)		
CRF part 3								
AE, SAE assessment	X	X	X	X	X	X	X	X
Phone call CRF part 4								X

4.9 Statistical analysis

4.9.1 Article I

Stata Statistical Software version 14.0 (StataCorp LP, College Station, Texas, USA) was used to analyse the results of article I. Numerical variables were summarised with means, ranges and standard deviations, and categorical variables were summarized using frequencies. To compare correlations between numerical variables, Pearson´s correlation coefficients were estimated. Results were presented with 95% confidence intervals. Since the data were clustered within individuals, all the inferential analyses were adjusted to take into account its clustered nature. $P < 0.05$ were considered significant.

4.9.2 Article II

Agreement in *phase one* was assessed using a Bland-Altman plot (including Pearson´s correlation coefficients between HR difference and HR values). Agreement in *phase two* and *three* was assessed using a Bland-Altman plot for repeated measures (including repeated measure correlation between HR difference and HR values), and in *phase three* using repeated measures version of kappa index on the following HR categories: less than 60, 60–99 and 100 bpm or above. The sensitivity and specificity of NeoTapLS in detecting bradycardia (HR less than 100 bpm) were also calculated. Acquisition times in *phase two* and *three* were summarized with median and inter-quartile range (IQR) for descriptive purposes. Statistical analysis was performed using R V.3.5 (R Foundation for Statistical Computing, Vienna, Austria).[154]

4.9.3 Article III

A 25% reduction in the primary outcome measure was considered to be clinically relevant for changing clinical practice. A sample size of 954 participants was required for a 90% chance of detecting a decrease in the proportion of patients with the primary outcome from 40 to 30% at a 2-sided significance level of 5%. The sample size was increased to 1150 to account for day-by-day cluster randomization, assuming an intraclass correlation coefficient of 0.10 and an average daily enrolment of 3 participants.

Intention-to-treat analysis was used for statistical purposes. Our protocol also specified a per-protocol analysis and a contamination (a switch to the other device) adjusted intention-to-treat analysis. However, we decided before unblinding not to perform these analyses because a switch to the other device occurred for safety reasons at the discretion of the provider and was likely to be associated with poorer outcomes.

Categorical data were recorded as frequency and percentage. Continuous data were recorded as median and IQR. The statistical analysis included both unadjusted and adjusted analyses. Outcome values were compared between the arms by the Chi Square test or Fisher's exact test (unadjusted analysis). Generalized mixed-effect models were estimated to measure the effect of the treatment on outcome, adjusting for clusters (random effect) and unbalanced participant characteristics (adjusted analysis). Effect sizes were reported as relative risk with 95% confidence intervals.

Data was rarely missing; hence the main analysis was based on complete cases. Post-hoc sensitivity analysis was also used on the primary outcome measure (with missing data counted as failures in LMA arm and as successes in FM arm).

All tests were 2-sided and $P < 0.05$ again was considered significant. Data were analysed using R software, version 3.5 (R Foundation for Statistical Computing, Vienna, Austria).[153]

5 Ethical considerations

5.1 Emergency research and consent processes

Neonatal resuscitation is carried out world-wide, but neonatal deaths mainly occur in low-resource settings due to improper birth care or neonatal resuscitation. Therefore, it is ethically relevant to conduct these studies in hospitals in low-resource settings. The *NeoSupra Trial* was run at Uganda's largest national referral hospital which has a high number of deliveries. This made it possible to recruit the necessary number of participants within a reasonable time frame, which is also ethically relevant so that research funding is not wasted. Emergency research with critically unwell neonates, as in the *NeoSupra Trial*, is vital to understand how these neonates can benefit from evidence-based healthcare.[155]

Ethical guidance requires that consent is sought from legal representatives on behalf of the neonates.[156] Ethical frameworks has been established to ensure an effective system for review of research under research ethics committees that were independent of government and sponsors.[157] This is to avoid suffering, show respect for cultural differences, and to prevent exploitation of the vulnerable. However, implementations of informed consent guidelines can also create barriers for getting potentially life-saving treatments in time.[158,159]

The decision to participate in research extends beyond individual consent and further research should assess how medical care offers affects the decision to participate in trials.[160] In the *NeoSupra trial*, a small travel compensation was given to all parents for follow-up visits, but no free medical care was offered.

Collecting informed consent in neonates needing PPV before starting treatment was impossible as it would delay the intervention and diminish the neonate's chance of survival. Furthermore, parents will usually be highly distressed in a critical care situation, and many will struggle to make an informed decision about research in the limited time available.[161,162] We searched the literature regarding consents in emergency research, which was followed by extensive discussions with clinical experts on the Mulago Hospital Research and Ethics Committee (MHREC).[158,161-170]

We agreed on a 2-tiered consent procedure. The procedure combined a prior brief oral consent with deferred consent - a possibility in potentially life-threatening situation suggested by existing guidelines and used in similar trials.[156,171] Written and oral information was given to all parents on maternal admission from dedicated RAs, unless the mother was distressed or in second stage labour. A senior investigator was available at any time to discuss further questions concerning the trial. Deferred consent was obtained post-hoc from those mothers whose neonates were eligible for continuing participation.

5.2 External monitoring, the *NeoSupra Trial*

In the *NeoSupra Trial* article III, an independent data monitoring committee (IDMC) operated according to DAMOCLES procedures.[172] In January 2019, a pre-planned interim analysis was carried out, allowing the trial to continue, which was conducted in accordance with the principles of the Declaration of Helsinki.[156]

5.3 Management of stillbirths, the *NeoSupra Trial*

To avoid misclassification and inclusion of fresh stillborn (born with no HR and breathing efforts), all neonates received at least 10 min ventilation. However, macerated neonates graded 0-1 (‘parboiled’ reddened skin or skin slippage and peeling) received only 1 min ventilation for ethical reasons.[173] To clarify when neonatal resuscitation efforts should otherwise be terminated, we turned to the ILCOR international consensus on neonatal resuscitation, 2015, the Ugandan Clinical Guidelines, 2016, and HBB 2nd edition, and created a local resuscitation flow-chart approved by the hospital management.[17,18,20,62,174] The flowchart was put on the wall of all 3 resuscitation tables during the entire recruitment process (Annex II). Health personnel were recommended to seek advice from doctor if there was no perceptible HR after 10 min or no spontaneous breathing after 20 min, even if the HR was adequate. A doctor would then take the decision to terminate the resuscitation. If no doctor was available, the health personnel were instructed to terminate the resuscitation themselves, following the time-limits of the flowchart.

5.4 Safety and harms, the *NeoSupra Trial*

Before the start of the *NeoSupra Trial*, standard operational procedures for the detection and reporting of AEs and serious adverse events (SAEs) were implemented. Rehearsals and 'dry runs' strengthened compliance to the protocol. AEs were defined as medical events that occur among study participants (resuscitated neonates) with or without a causal relationship with the use of resuscitation devices in the trial. SAEs were defined as AEs that: a) looked life threatening or resulted into death, b) required hospitalization or prolongation of existing hospitalization, c) were persistent or resulted in significant incapacity, d) were a disability not due to birth asphyxia, e) were an important medical condition based on the investigator's judgement and on the Ugandan Human Subjects Protection Guidelines.[175] Resuscitations were continuously monitored by video, observed by RAs and trial doctors to detect AEs and SAEs. Noted AEs were managed by hospital physicians and were followed until resolution or until a stable clinical endpoint had been reached. When the trial investigator became aware that an SAE had occurred, either expected or unexpected, and with or without any relationship to the use of the supraglottic airway, the appropriate SAE reporting form was completed as soon as possible, and a copy was submitted to MHREC immediately or in <7 days. Any Suspected Unexpected Serious Adverse Reactions (SUSARs) with or without a plausible causal relationship with the use of the LMA were also reported to the MHREC. A copy of the same report was emailed immediately to the trial sponsor. The incidence of SAEs was compared between the two trial arms by the IDMC during the interim analysis.

5.5 Approvals

The observational manikin study, article I, was approved by the Sachs' Children and Youth Hospital, Stockholm, Sweden.

The prospective observational study in 3 phases, article II, had different consent processes. In *phase one,* written informed consent was obtained from all low-end users (midwives). In *phase two,* written informed consent was obtained from the parents on maternal admission before admission to the operating room, and from high-end users. A senior investigator was available on the wards to discuss any

queries concerning the trial. Data was collected as a sub-study of the 'Randomized Clinical Trial Assessing Laryngeal Mask Airway Versus Face-Mask Ventilation in Neonatal Resuscitation (LMA vs FMV)' (ClinicalTrials. gov NCT02042118), approved by the Institutional Review Board (IRB) of Mulago National Referral Hospital, Uganda, the Uganda National Council of Science and Technology, the Director-General from the Ministry of Health, Uganda and the Regional Committee for Medical and Health Research Ethics in Norway, No 2013/2096. In *phase three,* written and oral information was given to all parents on maternal admission, and deferred consent was obtained post-hoc in cases needing resuscitation. These data were collected as a sub-study of the *NeoSupra Trial* (ClinicalTrials.gov NCT03133572) approved by the Institutional Review Board (IRB) of Mulago National Referral Hospital, Uganda, the Uganda National Council of Science and Technology, the Director-General from the Ministry of Health, Uganda and the Regional Committee for Medical and Health Research Ethics in Norway, No 2017/989.

6 Summary of results

6.1 Article I

The first study in this thesis explored the accuracy and speed of NeoTapLS that aims to assess a neonate's HR, showing that a simulated HR or pulse on a manikin could be accurately and rapidly assessed using the NeoTapLS. Thirty participants used NeoTapLS to determine 20 randomly selected simulated HRs by auscultation or palpation, 1200 simulations in total. As a true value, we used simulated HRs and pulses generated on a Laerdal SimNewB manikin that could present rates in multiples of 10. The estimated rates were arranged into 3 categories: very low (<60), low (60–99) or normal (100 or above) according to international guideines.[17] The simulated HRs were categorised into very low (20–50), low (60–90) or normal (100–140).

Auscultation

Of 600 simulations, we found a high correlation between estimated and simulated HRs across all categories (Pearson´s correlation coefficients = 0.993). The majority (93.5%) of auscultations differed by 5 beats or less from the true value. Only 3% of the estimated rates of simulated HRs were placed in a different category compared to the true value (Table 6), none being misclassified in the very low range. The estimations of simulated HRs at 60 and 100 were more prone to misclassification of category since they were cut-offs for the 3 categories. Excluding the simulated HRs of 60 and 100, only one was misclassified. The mean difference between the estimated and simulated HR was small, and the mean acquisition time for the estimated HR was 14.9 s.

Palpation

Of 600 simulations, was found a high correlation between estimated and simulated HRs (pulses) across all categories (Pearson´s correlation coefficients = 0.986). The majority (86.3%) of palpations differed by 5 beats or less from the true value. Some of estimated rates (6.5%) of simulated HRs were placed in a different category compared to the true value (Table 6). If we excluded the simulated HRs of 60 and

100, 9 were misclassified. The mean difference between the estimated and simulated HR was small, and the mean acquisition time for the estimated HR was 16.3 s.

Table 6. Simulated heart rate and estimated heart rate by auscultation and palpation, divided by categories, according to International Neonatal Resuscitation Guidelines.

		Simulated heart rate		
		Very low (20-50) N=210 n (%)	Low (60-90) N=120 n (%)	Normal (100-140) N=270 n (%)
Estimated heart rate <60	By auscultation	210 (100)	2 (1.7)	0 (0)
	By palpation	209 (99.5)	8 (6.7)	0 (0)
Estimated heart rate 60-99	By auscultation	0 (0)	117 (97.5)	15 (5.6)
	By palpation	1 (0.5)	111 (92.5)	29 (10.7)
Estimated heart rate ≥100	By auscultation	0 (0)	1 (0.8)	255 (94.4)
	By palpation	0 (0)	1 (0.8)	241 (89.3)

6.2 Article II

In article II, a study in 3 phases, we assessed rates and heart rates with the NeoTapLS app. Clinical HR assessment was very fast, but clinical assessment of neonates needing PPV by low-end users (midwives) was less accurate than for high-end user in neonates not needing PPV.

Phase one

In this simulation, 18 midwives made 180 recordings of a metronome rhythm using NeoTapLS. There was a mean difference of −6 bpm, with 95% agreement limits of −26 to 14 bpm. Recordings ranged from 21 to 131 bpm, and the metronome was set from 30 to 130 bpm. In total 77% differed by 10 or less from the true value and 95% differed by 20 or less.

Phase two

In this clinical study, one paediatric specialist assessed 69 HRs with NeoTapLS on 33 neonates not needing PPV compared to pulse oximetry. A mean difference of 3 bpm, with 95% agreement limits of −14 to 19 bpm, was found. HR ranged from 132 to 214 bpm with NeoTapLS, and from 126 to 205 bpm with pulse oximetry. In total 88%

differed by 10 or less from the true value and 96% differed by 20 or less. The median acquisition time for the estimated HR was 5 s. The characteristics of the neonates in *phase two* and *three* are given in Table 7.

Table 7. Characteristics of neonates in Article II, phase two and three.

Characteristics	*Phase two*	*Phase three*
Number of neonates	33	98
Number of recordings	69	235
Need for positive pressure ventilation (PPV)	No	Yes
Apgar 1 min	9 (IQR 9-9)	3 (IQR 2-4)
Apgar 5 min	9 (IQR 9-10)	5 (IQR 4-6)
Median weight (g)	3000 (IQR 2700-3390)	3100 (IQR 2750-3400)
Time heart rate assessments after birth (s)	120-1800 (median 300, IQR 180-600)	~100-720[a]

[a]*Exact data on time for measurements was impossible to obtain by the method used in phase three*

Phase three

Eighteen midwives assessed 235 HRs with NeoTapLS on 98 neonates needing PPV compared to ECG. A mean difference of 3 bpm was found, with 95% agreement limits of −48 to 53 bpm. HR ranged from 46 to 294 bpm with NeoTapLS, and from 46 to 229 bpm with ECG. In total 48% differed by 10 or less from the true value and 73% differed by 20 or less. NeoTapLS showed very good sensitivity (0.87) and specificity (0.96) in detecting bradycardia (HR <100 bpm; Table 8). The median acquisition time for the estimated HR was 2.7 s.

Table 8: Distribution in categories of correctly and incorrectly recorded heart rates among midwives assessing neonates needing positive pressure ventilation (PPV) compared to the electrocardiography in phase three

		Electrocardiography	
NeoTapLS	<60 bpm	60-99 bpm	≥100 bpm
<60 bpm	1	1	0
60-99 bpm	2	22	8
≥100 bpm	0	4	197

Data expressed as number of evaluations in each category

6.3 Article III

In this trial, 8.6% (1439) of the 16 791 neonates eligible for participation needed PPV at birth. The inclusion criteria were fulfilled for 1163 neonates; average cluster size was 3 neonates per 24 h cluster. After 9 lost to follow-up, 1154 were included in the analysis (Figure 22). Switch to the other device occurred in 3.5% in the LMA arm and 10.9% in the FM arm, the most common reasons being absent/poor chest movement and absent/poor HR improvement (article III Supplemental Appendix Table S1). Baseline characteristics were balanced between arms except for sex (article III Table 1).

The primary outcome occurred in 27.4% of neonates in the LMA arm and 24.4% in the FM arm (Table 9). Very early neonatal death occurred in 15.8% in the LMA arm and 14.4% in the FM arm. There was no evidence that any of the secondary outcome measures differed substantially between arms (Table 9). About 61% had meconium-stained and/or foul-smelling amniotic fluid. Few AEs occurred overall and there was no significant difference between the arms (article III Table 3). LMA did not reduce early neonatal death or moderate-to-severe HIE compared with FM in asphyxiated neonates. LMA was safe in the hands of midwives.

Neonates switched from LMA to FM were more likely to be admitted to the NICU for HIE compared to those first receiving FM and then LMA (article III Supplemental Appendix Table S1).

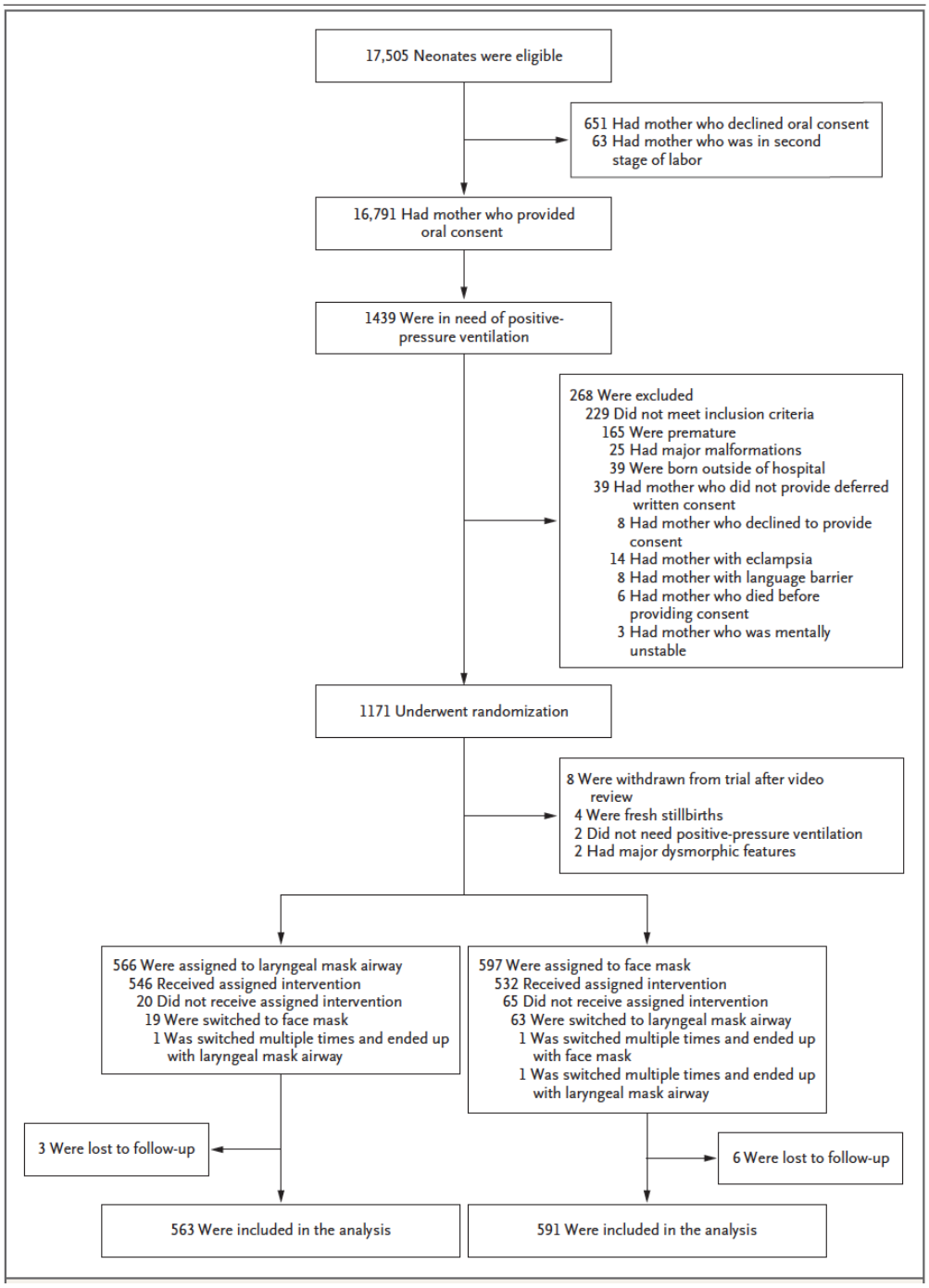

Figure 22. Enrolment and randomization of the participants. Published with the kind permission of The New England Journal of Medicine.

Table 9. Outcome measures. Published with the kind permission of The New England Journal of Medicine.

Table 2. Unadjusted and Adjusted Analyses of the Primary and Secondary Outcomes.*

Outcome	Laryngeal Mask Airway	Face Mask	Unadjusted Analysis		Adjusted Analysis†	
			Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no./total no. (%)					
Primary outcome	154/563 (27.4)	144/591 (24.4)	1.12 (0.92–1.37)	0.27	1.16 (0.90–1.51)	0.26
Secondary outcomes						
Advanced resuscitation	39/566 (6.9)	39/597 (6.5)	1.05 (0.69–1.62)	—	1.08 (0.63–1.86)	—
Early neonatal death	122/563 (21.7)	109/591 (18.4)	1.17 (0.93–1.48)	—	1.21 (0.90–1.63)	—
Very early neonatal death	89/563 (15.8)	85/591 (14.4)	1.10 (0.84–1.45)	—	1.13 (0.80–1.58)	—
Admission to NICU with Thompson score of ≥11 at days 1–5 during hospitalization	53/474 (11.2)	51/504 (10.1)	1.13 (0.89–1.70)	—	1.27 (0.84–1.93)	—
Admission to NICU with Thompson score of ≥7 at days 1–5 during hospitalization	100/474 (21.1)	115/504 (22.8)	0.97 (0.78–1.21)	—	0.94 (0.70–1.27)	—
Any hospital admission during first 7 days of life	496/519 (95.6)	530/554 (95.7)	0.99 (0.97–1.02)	—	—	—

* The primary outcome was a composite of early neonatal death (within 7 days) or admission to the neonatal intensive care unit (NICU) with moderate-to-severe hypoxic–ischemic encephalopathy (Thompson score, ≥11) at day 1 to 5 during hospitalization. Thompson scores range from 0 to 22, with higher scores indicating greater severity of hypoxic–ischemic encephalopathy. Very early neonatal death was defined as death within 24 hours.

† The analysis was adjusted for cluster and sex. Adjusted analysis for hospital admission was not performed owing to the small number of participants not admitted to the hospital. In a sensitivity analysis of the primary outcome measure (in which participants with missing data were counted as having had a primary outcome event in the laryngeal-mask-airway group and as not having had such an event in the face-mask group), the unadjusted relative risk was 1.15 (95% CI, 0.95 to 1.40).

6.4 Suction practices

In a sub-study of the *NeoSupra Trial* that included 46 participants, we collected more detailed data using a respiratory function monitor and video-reviewing. Suction was performed on 52.2% of the participants in the LMA arm and 56.6% in the FM arm. The median suction duration was 30 and 29 s, respectively. Obstruction of the airways with poor chest movements, low tidal volumes and bradycardia were recorded in 17.4% of the LMA cases and 47.8% of the FM cases (unpublished data). Of the 46 participants, 10 (22%, 4 in the LMA arm and 6 in the FM arm) received deep oral and/or tracheal suctioning with a modified Laerdal Penguin (Figure 23), improving HR and expired tidal volumes in all the treated participants. It seemed that severe mucus plugs caused the airway obstruction, insertion of LMA not resolving the problem.

Figure 23. Laerdal Penguin suction device adapted for endotracheal suctioning. Photo: N. Pejovic.

7 Discussion

This thesis reports the development and investigation of innovations and new strategies in supporting neonatal resuscitation in low-resource settings, in which most neonatal mortality and morbidity occur. The findings will be discussed in the following order:

- Innovations and new strategies
- Heart rate assessment at birth
- Laryngeal mask airway as primary device in neonatal resuscitation
- Task-shifting heart rate assessment and laryngeal mask airway use to midwives
- ILCOR 2020 Consensus on Sciences with Treatment Recommendations
- And what about suction?
- Methodological considerations
- Other biases
- Trials and the effect of new tools
- Emergency research
- The impact of a pandemic on neonatal mortality

7.1 Innovations and new strategies

The SDG 3.2 aims for a neonatal mortality rate of ≤12 per 1000 live births in all countries of the world before 2030, but many countries are lagging behind. State-of-the-art neonatal resuscitation saves lives and also needs to be implemented in low-resource settings, having high neonatal death rates. Current guidelines do not provide an alternative way to accurately assess HR where Doppler, pulse oximetry or ECG is unavailable. FMV is a difficult skill that cannot solve all airway problems. LMA is recommended when FMV proves unsuccessful, or where there is a lack of skills or equipment to insert an ETT.

In low-resource settings, midwives are still in charge of neonatal resuscitations; one cannot rely only on doctors being available to evaluate neonates and initiate or

maintain PPV. New data reports that an Apgar score at 5 and 10 min provides prognostic information about neonatal survival among preterm neonates.[176] It is important that these scorings are based on good clinical examination by midwives. In referral hospitals of these settings, a high number of neonates need resuscitation at birth. Health personnel responsible for neonatal resuscitation need to be trained to master evaluation of HR and airway access since they are on the front line of these healthcare systems.

7.1.1 mHealth apps and HR assessment

Innovations and new strategies are of great importance for improving neonatal health, as highlighted in recent reviews.[55,89,92,107,108,177] However, many factors influence the care that midwives can provide to neonates in low-resource settings. Implementing proven techniques, training existing health personnel sufficiently and providing midwives with already existing equipment and a good working environment, are probably the most important factors to get into place to reach the SDG 3.2 by 2030.[55]

A qualitative study in Uganda in 2012 described the urgent need for in-depth understanding of knowledge translation of evidence-based interventions in low-resource settings.[109] Access to resources, commitment and community involvement are important in successful translation of knowledge and techniques.

Global scale-up of the HBS initiative has been rapid and numerous bottlenecks, gaps and barriers having been highlighted.[69] The HBS programme has now been scaled-up for a decade, and at the same time mobile phone ownership and access to cellular networks have increased quickly in low-resource settings. One report has described a number of HBS digital health innovations and resources developed between 2010 and 2020 to support education and training, data collection for monitoring and evaluation, clinical decision support, and quality improvement.[178] The authors concluded that thoughtful integration of purpose-built digital health tools, innovations and resources can assist HBS practitioners to more effectively disseminate and implement neonatal care programs. None of these innovations had incorporated the NeoTapLS tapping technique for HR assessment.

However, the Liveborn app (Laerdal Global Health, Stavanger, Norway, freely downloadable on Google-play and App-store) launched in 2019 is one of these new apps supporting HBB implementation that actually has a HR monitoring option. The Liveborn app is used for live observation of neonatal care the first minutes after birth, similar to the NeoTapAS app. A recent review states a need for consensus guidelines and innovative solutions in the documentation of neonatal resuscitation.[179]

Using Bluetooth technology, the Liveborn app can stream HR from the dry-electrode ECG NeoBeat. Apart from this feature, the app has manual registration of breathing status of neonates, and provider interventions and post-observation case summary. It is part of the Laerdal Safer Births Bundle serving to support healthcare workers and health systems globally to deliver better quality of care at birth, with increased efficiency and accountability. The Liveborn app have now been used at 12 hospitals in 4 countries between April 2019 to March 2020, and about 18 000 births have been observed, including 500 neonates needing PPV, but data are not yet available.

7.1.2 Hypothermia treatment

The NICU in our setting had no resources for therapeutic hypothermia, but new innovations in this area are under investigation that may overcome the issue of power shortage and long transports in the future. Examples of this are ice-packs and phase changing materials. These low-cost devices are safe and effective alternatives for maintaining therapeutic hypothermia in low-resource settings with adequate monitoring, but their impact on neonatal mortality and HIE in low-resource settings have still to be evaluated after further investigation.[180,181] One must also be aware that neonates with severe HIE are more often subject to hypothermia due to passive cooling (drop in body temperature postpartum) than healthy neonates. This passive cooling must be taken into account when designing future clinical trials for low- and middle-resource settings.[182]

7.1.3 Implementation of innovations and new strategies

Implementation of innovations and new strategies lies beyond the scope of this thesis, but still is important to consider. For example, cardiorespiratory monitoring devices

are promising, but to understand their impact on neonatal outcomes in low-resource settings, early adopters should share their experiences broadly for better understanding of any implementation barrier.[183]

NeoTapLS and NeoTapAS were developed with few app alternatives available on the market at the time. However, time has shown that mHealth tools are under investigation for implementation in low-resource settings. The *NeoSupra Trial* gave our team a unique insight into the context in a busy referral hospital, in sub-Saharan Africa, where midwives work. Our observations on NeoTapLS, the *NeoSupra Trial* (articles I-III), and upcoming investigation of mHealth apps will bring more clarity to innovations and new strategies in neonatal resuscitation in low-resource settings.

7.2 Heart rate assessment at birth

Measurement of HR at birth is important not only in assessment of the neonate needing PPV but is essential to avoid misclassification. A debated area in low-resource settings is 'fresh stillborn'. Annually 2.6 million stillbirths are reported, half being after the onset of labour.[46,184] In Nepal up to 46% of intrapartum stillbirths were potentially misclassified.[185,186] I chaired a qualitative focus group discussion in 2018, involving 44 midwives working at the High-risk Labour Ward and Operating Theatre, Mulago National Referral Hospital, Uganda.[187] The group found that midwives had neither the knowledge nor the equipment to measure HR with a stethoscope at birth before the start of the *NeoSupra Trial*. They only palpated the cord or the chest to decide whether a neonate was alive (unpublished data). This technique is unreliable since deeply compromised neonates may not present with a cord pulse even if the heart is still beating.[81] This may mislead health personnel in believing that the neonate is dead, and thereby misclassify him/her as a stillbirth even though proper PPV might have saved the neonate.

A HR of 100 is the cut-off for normal HR and guides the resuscitator to re-evaluate ventilation and a HR of <60 suggests one should start heart compression according to the ILCOR guidelines.[17,18,20] Reference to a normal HR in the first min after birth not needing PPV was investigated in 2010.[14] The data were obtained by pulse oximetry, a method that might underestimate the HR compared to ECG.[188] The study indicated

that many neonates not needing PPV meet the criteria for interventions. A systemic review in 2019 reported again that pulse oximetry and ECG were precise, but took a considered amount of time to apply to the neonates.[189] Using dry-electrode ECG, it was reported that HRs of <100 bpm were uncommon in neonates not needing PPV, accounting for <5% of neonates at 30 s after birth.[190] For half of the neonates, the HR was detected from 13 s after birth, and 75% from 22 s, showing dry-electrode ECG to be a quick method. This further highlights the fact that incorrect estimations of HR could lead to impropriate management, and that precise, fast and easy-to-use methods are needed.

7.2.1 Rate assessments in simulations by NeoTapLS

The manikin study (article I) gave fast and accurate assessment of a simulated HR using NeoTapLS by 30 participants of different background, the first study of its kind. The metronome study (article II *phase one*) reported accurate assessment of a metronome rhythm by midwives using NeoTapLS. Furthermore, midwives overestimated low rates and underestimated high rates, which could be explained by anticipating that in low rates it is easy to tap too early, and in high rates it is difficult to maintain the high speed. Prior to the metronome study, one simulation study also reported that HR could be accurately and rapidly assessed using NeoTapAS (the Ipad version) on a manikin.[191] In 2019, a randomized simulation trial showed that NeoTapAS reduced the time to the first HR, initiation of heart compressions and administration of epinephrine compared with auscultation and mental computation.[192] Following this, the use of a porcine model showed that HR assessment with NeoTapAS had a similar accuracy compared with auscultation using a digital stethoscope, ECG or carotid blood flow during asphyxia, and a faster acquisition time compared with the 6 or 10 s method with a digital stethoscope, wherein HR is calculated by multiplying the number of heartbeats heard in 6 s by 10 or in 10 s by 6.[193]

Prior to these studies, auscultation and palpation had led to incorrect management. Four reviews have pointed to problems regarding the inaccuracy of existing methods.[89,92,177,189] A randomized simulation showed that up to 28% of simulated

HRs obtained by auscultation led to incorrect management;[83] and another simulation study reported that HRs of <60 bpm were inaccurate, giving overestimates.[84] A prospective, randomized controlled study showed that errors in initial HR determination occurred in 26–48% of cases; an error in HR assessment was defined as a HR that differed by at least 15 bpm from the actual HR set on the simulator.[82]

Our simulation studies showed that very few estimations fall on the wrong side of the cut-off levels, i.e. 60 and 100 bpm, and made it unlikely that it would lead to differences in the management of the neonate during resuscitation.

7.2.2 Heart rate assessments in clinical use by NeoTapLS

The clinical observations (article II *phase two* and *three*) indicated variable accuracy and precision in estimating HRs with NeoTapLS in HR auscultation, especially for midwives. The midwives could quickly learn the tapping technique and had very short acquisition times. The previous observation that midwives overestimated low simulated rates and underestimated high simulated rates was not seen in the clinical study. Data on the clinically important group of HR <60 bpm were few and show divergent results. This problem needs further investigation. In clinical use, this effect may be problematic at low HR, but with high HR it has minor implications as it does not change clinical decision-making. A new observation in clinical use was that a few recordings by midwives in *phase three* seemed to be twice the actual HR. This is an important finding, from which it is speculated that some midwives, inexperienced in listening to heart sounds, tapped on both the first and second heart sounds, i.e. tapping twice for a single heartbeat. This poses an obvious risk for errors in HR assessments by auscultation, independently of the use of NeoTapLS.

Acquisition times were possibly too short in *phase three*, median 2.7 s, due to a misunderstanding of the 'tap at least 3 times for HR' feature of the app. NeoTapLS users should be reminded to tap until they are sure that they are tapping the same pace as the HR heard when auscultating the heart or palpating the pulse, the algorithm of NeoTapLS displays the average rate of the last 3 taps.

Novel technologies including tap-based applications can support HR assessment[150], but their clinical effectiveness during neonatal resuscitation needs to be further investigated. No other studies were found on HR assessments during neonatal resuscitation with nondoctoral health personnel.

Our clinical study reported very few HR estimations that fell on the wrong side of the cut-off levels, making it unlikely that it could lead to differences in the management of the neonate during resuscitation. The results also showed that NeoTapLS was much faster than pulse oximetry and ECG. The findings add valuable information on NeoTapLS feasibility in clinical use.

Awareness of the first and second heart sounds is essential; clinical studies have shown that training is crucial, with repeated training of health personnel affecting the management of patients.[194,195] It is likely that clinicians would have obtained better results due to prior experience in HR auscultation.

If midwives are trained to use a stethoscope, with the assistance of NeoTapLS, evaluation of HR may be more appropriate at birth and during PPV. This may lead to a decrease in interruption of ventilation and may be an alternative to expensive medical equipment. NeoTapLS may also be used for foetal HR monitoring. The inconsistent capacity to provide advanced resuscitation by local health personnel in our setting limits generalisation of the findings to better resourced settings. Future studies, including clinical trials that compare smartphone-assisted HR estimations to pulse oximetry or ECG, should provide more data on the potential of NeoTapLS prior to clinical use.

7.3 Laryngeal mask airway as a primary device in neonatal resuscitation

Prior reports, including a Cochrane review, have indicated that the use of LMA in neonatal resuscitation results in shorter ventilation times and faster pick-up in HR compared to FM.[114,131,196-198] These studies were conducted in populations of mildly asphyxiated neonates. Resuscitations in previous studies were invariably carried out by doctors using LMAs with an inflatable cuff.[136,197,199,200]

Our hypothesis was that a cuffless LMA as the primary device reduces early neonatal mortality and morbidity, even when used by midwives. In our setting with a high proportion of deeply compromised neonates of which 8.6% needed PPV, a safe and efficient airway access from the start of PPV could be of significant importance, since very early neonatal deaths were common. Comparing these numbers with previous reports[2,201] suggests that our setting involved a sicker population, reflecting the hospital demographics, with a large number of late referrals. The limited resources at the NICU- for example, no access to therapeutic hypothemia treatment – may have a negative impact on the survival of these deeply compromised neonates.

We had a higher rate of failure in treatment of the FM arm and more cases of LMA rescue, consistent with previous trials (article III Supplemental Appendix Table S1).[114,197,198] The skills of the midwives changed - possibly improved - before and during the trial as a result of prior HBB training and repeated on-the-job training. More health personnel were present during the trial, and we task-shifted HR assessment to the midwives by providing them with personal stethoscopes. It was obvious that FMV skills improved among the midwives during the trial. This may explain why our trial did not demonstrate superiority of the LMA over FM but will be further investigated in upcoming video-review sub-studies to the *NeoSupra Trial*. The trial was not designed to assess non-inferiority of LMA use compared to FM meaning testing if the intervention arm is not worse than the control arm. The findings support current ILCOR recommendations.[202,203]

This trial had a large number of subjects and a rigorous methodology, including video documentation, strong adherence to arm allocation and minimal loss to follow-up. It has extended our knowledge about the use of LMA among severely compromised neonates in a low-resource setting. It followed the CONSORT guidelines and thus help to guide future protocol.[142,204] The results indicate that LMA can be safely used by trained midwives as an alternative device in neonatal resuscitation. LMA did not reduce early neonatal death or moderate-to-severe HIE.

7.4 Task-shifting heart rate assessment and laryngeal mask airway use to midwives

In many places in the world, non-doctor health personnel are the first to assess a neonate. High-volume referral hospitals in low-resource settings have a high delivery rate and a low number of health personnel, making it a challenging environment in which to implement complicated interventions. Midwives in these settings need our full attention if we are to reach the SDG 3.2 goal. Relying on doctors to save neonates in need of advanced resuscitation is unrealistic; it requires a new system of on-call service of doctors 24/7, as in high-resource settings, although this is unlikely to be before 2030. In obstetrics, innovative training of a mid-level workforce has improved accessibility of emergency care, including major surgery such as caesarean section, in low-resource settings. Data shows that outcomes are equal to surgery intervention by doctors, and these mid-level providers had a very high retention rate, i.e. it is a cost-effective implementation.[205]

As discussed above, inaccurate HR assessment can result in inappropriate actions. Not auscultating the heart could even mislead health personnel to think that a neonate is stillborn when, in fact, it is alive. The HBB 2nd edition does not teach one how to assess HR, even if the training kit includes a plastic stethoscope. Most health personnel in low-resource settings do not have full knowledge and skills to properly measure and assess the HR accurately, and most lack a suitable stethoscope. In my qualitive study, midwives said that stethoscopes are at present used by doctors, but they wanted to learn to use them.[187] Auscultation-focused training and awareness of the first and second heart sounds could potentially improve clinical HR assessments by midwives; they need to be part of HBB training and in the routine assessments done by midwives.

When starting the *NeoSupra Trial,* no prior trial using LMA had involved unsupervised midwives. Video filming was used for safety when midwives for the first time used the LMA unsupervised; the results showed few AEs. Our data support a smooth transition to midwives using LMA, neither should the step to introduce it to midwives in low-resource settings be controversial. The *NeoSupra Trial* provided

solid evidence that skills acquired from LMA insertion on the manikin translates into good clinical practice.

PPV with FM leads to many interruptions, >30% of the total ventilation time in high-resource settings.[96] LMAs, once inserted, could result in fewer interruptions, which may be beneficial to the neonates. LMA ventilation can also be done with one hand, an advantage in low-resource settings where there are fewer health personnel.

A cuffless LMA was used in the *NeoSupra Trial* to create an efficient seal with the gel cushion to the larynx. This cuffless LMA is easy to position, with the risk of tissue damage or dislodgement being low.[131,206] This makes it an ideal device in settings were ETT is unavailable.[49] The cuffless single-use LMA used in this trial is currently too expensive for large-scale implementation, and multiple use options with inflatable cuff might be more feasible, although with the risk of delaying PPV, and therefore needs further investigation.

In a large randomized controlled trial (RCT) comparing LMA versus ETT in paediatric anaesthesia, the ETT arm had 5 times more AEs than the LMA arm.[129] Our phase II trial on LMA versus FM showed no AEs and the *NeoSupra Trial* had few AEs (2 cases of blood from mouth in each study arm, and no cases of laryngospasm or vomiting, article III Table 3). Few AEs confirm previous results, from which it can be concluded that LMA is safe in the hands of midwives.[114] However, in a recent manikin study, proficiency in the insertion of LMA equivalent to the ETT was not apparent.[207] Further studies need to investigate if and when LMA can replace ETT, which would give further support to LMA as a device suited for settings where midwives are in charge of neonatal resuscitation.

7.5 ILCOR 2020 Consensus on Sciences with Treatment Recommendations

The ILCOR 2020 CoSTR has been published without changes to the 2015 recommendations related to HR assessments and the use of LMA.[202,203] The report identifies 7 studies related to HR, including 2 reviews, published after the ILCOR 2015 CoSTR systematic review.[85,177,189,208-211] According to the ILCOR, the 2015 treatment recommendation was fully supported. The ILCOR suggests ECG is used to

provide a rapid and accurate estimation of HR, although the recommendation is weak and based on very poor evidence. A critical review of the 2020 ILCOR CoSTR did not agree with the authors claiming these studies support the 2015 recommendation.[212] They stated that several of the studies quoted do not recommend the use of ECG alone. They also pointed at a recent review from Tanzania demonstrating signals from ECG dry electrodes obtained as late as a median of 102 s after birth.[213] The problem of pulseless electrical activity, a phenomenon that occurs when cardiac output is zero while the ECG still displays an HR, has also been highlighted.[150] The review argues that The American Heart Association recommendation is more appropriate in stating that: "Auscultation of the precordium remains the preferred physical examination method for the initial assessment of the HR. Pulse oximetry and ECG remain important adjuncts to provide continuous HR assessment in babies needing resuscitation".[214]

Of note, the ILCOR upholds the need for new HR monitors, such as digital stethoscopes, photoplethysmography, Doppler ultrasonography methods with auditory or visual displays, and new interfaces for ECG monitoring, including dry-electrode technology. They suggest that future CoSTR systematic reviews ought to compare these technologies to the current "gold standard" of ECG monitoring. They do not mention tap-based smartphone apps, even if they are discussed in one of the 2 included reviews and released since 2015.[177] LMA for neonatal resuscitation was not reviewed in 2020, the recommendations remaining the same.

How proper HR and PPV are to be assessed in low-resource settings where training and adequate equipment may be lacking is still to be defined by the ILCOR.

7.6 And what about suction?

Suction-practice in neonatal resuscitation has been debated for years. Before the 2nd edition of HBB was launched, our team collected data by video-recordings on 99 neonatal resuscitation at the Mulago National Referral Hospital in 2016.[145] Suction practice did not follow the HBB guidelines and was delaying the start of PPV in the delivery room (median start of PPV 163 s, IQR 141-202; unpublished data). HBB 2nd edition de-emphasized suction, and during the *NeoSupra Trial* training prior to the

start of the trial, we put special emphasis on avoiding prolonged suction and the starting of ventilation within 60 s after birth. But in a subgroup of the *NeoSupra Trial* cohort in which we collected data with a respiratory function monitor, we found mucus plugs caused airway obstruction during neonatal resuscitation in 22% of the cases. These cases needed aggressive suction seldom seen in the high-resource setting were the principal investigators usually work. The neonates recovered quickly after removal of the plugs with deep suction using a modified Penguin Suction Device (Figure 23), which would not be the case in meconium aspiration syndrome. The literature on suction does not highlight this issue but focuses on routine clearing of the airways before the start of PPV, as in HBB.[215-218] Insertion of LMA did not seem to solve this clinical problem. In this population of severely compromised neonates, mucus plugs can be more common than in high-resource settings where there is better obstetric care. Active suction systems are rarely available in low-resource settings, but midwives can learn a deep suctioning technique that does not require active suction systems.

7.7 Methodological considerations

7.7.1 Methodological issues in the simulation studies, NeoTapLS

Design of simulation studies has its limitations. It is close to an ideal situation, a controlled environment with limited stress, no interfering sounds or movement of the neonate, but it does not reflect the challenging environment of emergency care of neonates. However, it is always best ethically to test a new method in simulations before moving to clinical studies.

In the simulations in article I and article II, *phase one,* one may consider the following methodological issues:

- Article I: we used a high-fidelity manikin with HRs and pulses, but did not apply breathing movements
- Article I: the manikin could only show numbers in multiples of 10
- Article I: we used 30 participants from different professions, the selection being done on site, depending on who had the time without any randomization

- Article II *phase one*: a metronome does not reflect the sound of a heartbeat
- Article II *phase one*: we had few recordings and limited the rates to 30–150 bpm

7.7.2 Methodological issues in the clinical studies, NeoTapLS

The design of clinical studies has other limitations compared to simulations. The setting is appropriate, but it is difficult to control the environment. However, clinical testing is essential to evaluate the feasibility of a method.

In the clinical studies in article II, *phase two* and *three,* one may consider the following methodological issues:

- Users and neonates were different for practical reasons
- Included midwives had limited experience of HR auscultation
- Participants in both phases were not masked to the true value
- The true value was different for practical reasons
- *Phase two* had a limited number of measurements for practical reasons, which was when investigators were on site in Uganda
- *Phase three* had a large number of assessments, but was uncontrolled and unsupervised; timing of ECG and HR assessment was up to the user
- We had few measurements of HR of <100 bpm and especially <60 bpm

7.7.3 Bias considerations in the observational studies, NeoTapLS

Bias is a *systematic error* due to design or method used affecting the interpretation of results. The main types in observational studies are *selection* and *information bias*. *Random errors* should be distinguished from *bias and* are related to the population and their impact on the results.

Selection bias occurs when the participants included differ from eligible participants, affecting any generalization of the results.

In article I, we included participants with a wide range of clinical resuscitation skills, but who were unfamiliar with the app. We disregarded any prior experience in smartphone management. The selection was done on site, depending on who had time

- all the people approached agreed to take part in the study. No prior information about the study had reached eligible participants, which limits the possibility of potential selection bias.

In article II, *phase one* and *three,* we selected all midwives employed as RAs in the *NeoSupra Trial*, and unfamiliar with the app. They were skilled in neonatal resuscitation and trained according to HBB 2nd edition as part of the *NeoSupra Trial*. They had limited training in auscultation of HR in neonates. We disregarded any prior experience in smartphone management, and all agreed to take part in the study. These midwives worked clinically at the labour wards and were therefore representative of the group. Although, they had all been involved in prior research projects, and therefore they would probably have a higher level of training and experience than the rest of the midwives at the hospital. This could have led to better performance in the selected group than the general group of midwives in Uganda. However, also these midwives had limited experience in HR auscultation. We do not know the results on less experienced health personnel in rural areas. Their performance would probably have been inferior.

In article II, *phase two,* we selected 2 paediatric specialists well familiar with the app. These physicians were not representative of a wider group of physicians or midwives at the setting and therefore a potential selection bias might have influenced the results. These doctors probably have better skills than other doctors at the trial site, which is a weakness of the study. Neonates not needing PPV were selected only when the 2 specialists were on site in the daytime, possibly introducing potential selection bias since more staff are already there overlooking the births, leading to less distressed neonates.

In article II *phase three,* we collected data from videos, in which only the hands of the midwives were seen. There is a risk that not all 18 midwives were included in the data-collection, but since they were all on duty during the inclusion-period and 98 resuscitations were included, the risk was negligible. There was also little risk that the midwives appearing in the videos differed in skills from the rest of the group.

We included all neonates needing PPV with simultaneous data from NeoTapLS and ECG during the study period, day and night, minimizing potential selection bias.

Information bias refers to systematic errors in measurements, also referred to as *measurement bias*.

Article I had 20 fixed true values in multiples of 10 on the manikin given as HRs and pulses. The participants were unaware of the limitations of the rate of the manikin, and this was unlikely to have affected the results. Participants were briefly introduced to NeoTapLS before the start of the study. The simulations could have been closer to a real scenario if we had added breathing movements, but the setup was designed to prove a concept and can be regarded as the equivalent of an in-vitro study in pharmacological trials. We did not separate the participants in the analysis of the data.

As in article I, article II *phase one* had fixed true values from a metronome, equal to all participants. The metronome had no limitations in its rate; the range was set to 30–150 bpm, but the midwives were not given this information. Midwives involved were briefly introduced to NeoTapLS before the start of the study, in which design minimizes the risk of potential information bias.

The participants were not blinded to the true value in article II, *phase two* and *three*, adding potential information bias. It was possible to keep on tapping until the number was close to that given by pulse oximetry and ECG. However, the algorithm of NeoTapLS displays the average rate of the last 3 taps. The very short acquisition times de-emphasizes this point.

In article II *phase two,* we used pulse oximetry as the true value. Pulse oximetry can display too low a HR during the first min of life.[188,209,210,219] However, pulse oximetry data was collected at 120 s or more after birth, supporting the reliability of the results. However, it may have introduced a potential information bias.

In article II *phase three,* we used ECG as the true value. This technique is recommended as gold standard by international guidelines because it is fast and

accurate, but technical issues, such as wet skin of the neonates, could also introduce potential information bias.

NeoTapLS introduces a potential information bias because it is up to the assessor to decide the time and the number of tapping on the screen needed to estimate the HR. The midwives in article II *phase three* did not assess the HRs directly when the neonates arrived at the table, and therefore probably missed checking HRs <60 bpm.

Random errors should be distinguished from bias and are related to the population and their impact on the results. This effect can be decreased by a bigger sample size. A prospective approach was used in our observational studies to limit errors since retrospective studies are more prone to random errors. We also made a large number of simulations with no missing values.

The firm methods and the lack of missing values in the simulation studies made the results trustworthy. Simulations indicated that moving to clinical studies was appropriate. Since the clinical results were accurate, swift and significant for doctors, it indicated that the app was user-friendly for a skilled group. The results for midwives were less accurate. However, the fact that true value, users and neonates were different, and the control over numbers in the clinical phases was limited, make it hard to generalise from the results. The great number of neonates involved gave us an indication on the limitations of NeoTapLS, and what requires further investigation.

7.7.4 Methodological issues in the clinical trial, the *NeoSupra Trial*

Studies that assign participants randomly into intervention or control groups are the RCTs, which are the best design to prove causality, i.e. the relationship between cause and effect. The design only allows us to look at the difference between the groups in terms of outcomes; if the randomization is done properly, it provides an unbiased assessment of the effects and safety of an intervention. Nevertheless, this design does not eliminate all potential errors at every level of the trial.

A Cochrane Collaboration assessment tool to identify potential biases in trials showed low risk of bias arising from the randomization process, deviation from

intended intervention and selection of the reported results, and high risk of potential bias due to missing outcome data and measurements of outcomes.[220]

In article III, the *NeoSupra Trial,* one may consider the following methodological issues:

- The participants were cluster-randomized to treatment by 24 h periods, for practical reasons
- It was a single-site trial in a high-volume referral hospital of severely asphyxiated neonates
- We had additional health personnel on site for safety reasons
- The midwives knew the allocation of the day; blinding was not possible
- Some switches occurred between arms as part of the trial design
- There was limited training in managing advanced resuscitation by local health personnel
- Outcome assessment of HIE was made by Thompson score without advanced exams, such as aEEG or cranial ultrasound
- Lack of appropriate foetal HR monitoring made the initial distinction between stillbirth and live birth difficult

7.7.5 Bias considerations in the clinical trial, the *NeoSupra Trial*

Three major categories of errors are often mentioned in clinical trials: *bias*, *confounding factors* and *random errors*.

Selection bias is introduced if the assigning of participants is not appropriate leading to a difference at baseline between the populations in the study arms. This can be solved by a solid design in randomization and selection. In this trial, we used randomization by day, each day representing a cluster. The randomisation list was generated by an independent statistician before the start of the trial, using block sizes of 4 to 8, dated and concealed until the assigned study day. The number of clusters was very high (>400) and the cluster size was small (only 3 neonates per cluster on average). This randomization method and the emergency nature of neonatal resuscitation limit any potential selection bias.

The participant characteristics of the *NeoSupra Trial* were a population of severely asphyxiated neonates. It may not represent the population of asphyxiated neonates at large, but rather as a subgroup of the 'worst affected'. The staff was also larger than normal for safety reasons. It is therefore uncertain whether the results can be generalized. Results from multi-centre trials are more solid to prove generalizability.

Study management or performance bias is introduced when the blinding, procedure and training are inappropriate.

In this trial, midwives performing neonatal resuscitation where not blinded to the intervention arm. Allocation concealment was in place but was given to the whole team each morning at 8:00 am. This knowledge of allocation could potentially have affected their behaviour in the day. If so, it was not obvious which direction this potential bias would go. The LMA had been introduced to the study site in a previous trial,[114] and was favoured by some midwives. Others may have felt uncomfortable with the new device and favoured FM. The hypothesis of this trial may also introduce a belief that the LMA is a life-saving device; this may have led to unnecessary switches from FM to LMA. International guidelines state that if PPV with FM is ineffective, or if intubation is not successful, LMA may be used as a rescue airway. Health personnel were trained and advised to follow international recommendations and continue with the device of the day for 3 min, which may have limited any potential bias.

Switches between groups may have contributed to improved outcome. Intention-to-treat analysis is a method for analysing results where all randomized participants are included in the statistical analysis according to the arm to which they were originally assigned. If an intervention is truly effective, an intention-to-treat analysis will provide an unbiased estimate of its effectiveness. Understanding the effect the intervention has on patients is critical for decision-making, both in individual patients and populations. Intention-to-treat analysis is therefore the most appropriate way of informing a health policy issue. A per protocol analysis would have potentially biased the results, since switch to the other device occurred for safety reasons and was likely to be associated with poorer outcomes.[221,222]

Limited training in managing advanced resuscitation by local health personnel also introduced limitations to the trial. We could not fully understand why the neonates died, and the assessment of surviving neonates by Thompson score were up to the individual assessor without firm outcomes. This potential bias is negligible in RCTs because they are likely to appear equally in both arms.

Detection bias can occur during outcome determination by both investigators and observers, and adds a systematic difference between the study arms, however blinding of outcome assessors could reduce this potential risk. NICU physicians assessing HIE outcomes and the statistician were blinded to the arm allocation, limiting the risk of potential detection bias. The Thompson score was not confirmed by findings from aEEG or neuroimaging and could have been underestimated or overestimated. This potential bias and lack of appropriate foetal HR monitoring does not matter so much in RCTs, since they are likely to appear equally in arms. We also limited this potential bias by dry-runs prior to the start of the trial to test the method.

The *NeoSupra Trial* had a low risk of potential ***volunteer bias*** in that the participants may not be representative due to few being unenrolled and a minimal loss to follow-up.

Attrition bias is a systematic error caused by unequal loss of participants from the study arms. Participants might withdraw due to AEs or death. This risk was obvious because of our 2-tiered consent procedure, further discussed in the section on emergency research (section 7.10). Potential attrition bias did not affect this trial; there was minimal loss to follow-up, 3/566 in the LMA arm and 6/597 in the FM arm.

Publication or reporting bias occurs when the dissemination of research findings is selected after inclusion of the data. To mitigate this selection, we published our outcomes at *clinicaltrials.gov* prior to starting the trial and published the study protocol before finishing the inclusions of participants.[142] We published the results, including those which did not support our hypothesis.

Potential confounding factors that cannot be held constant are, for example, the size of neonates and their sex. Randomization is supposed to control these factors by

generating comparable groups. We had a larger number of males than females in the LMA group. Male gender tends to be associated with increased risk of prematurity, respiratory distress syndrome and intrauterine growth restriction, with poorer outcomes than female neonates.[223-227] We therefore adjusted for sex in the analysis.

Random errors can be caused by numerous things, such as imprecision or inconsistencies in equipment used for data collection. These were considered and minimized by a large sample size.[142] High-definition video recordings of all resuscitations, scanning of CRFs, double-data entry and extensive data cleaning further limited the risk of random errors since we could review and correct errors from the video recordings. The Apgar score was subjectively assessed on site and not double-checked by video. The fact that the reliability of the Apgar score is questioned introduced potential random errors.[72]

The *NeoSupra Trial* had a high number of participants, well balanced groups and essentially no missing outcome data. The *NeoSupra Trial* has low risk of potential bias arising from the randomization process - deviation from intended intervention, selection of the reported results, and low risk of potential bias due to missing outcome data and measurements of outcomes.

7.8 Other biases

In article II *phase three* and article III, we video-filmed all the resuscitations carried out by the midwives. They were aware of the filming and the cameras were visible at the resuscitation tables, although at 2 tables had been hidden behind a warmer. The *Hawthorne effect* is as a consequence of participants being aware of being studied, which may affect their behaviour, i.e. the participants might actively drive the results towards the wishes of the researcher, a social equivalent to the 'placebo effect'. In our trial, we have not actively evaluated this effect, which may have introduced a potential bias.[228] However, even if the *Hawthorne effect* is involved, our impression has been that the midwives soon forgot about the cameras. This could be an effect of the emergency of the intervention, giving no time to reflect on filming of the events.

7.9 Trials and new tools effect

Performing a trial impacts on the study site in numerous ways affecting both arms. In the *NeoSupra Trial,* the awareness of neonatal resuscitation was increased by the training, the supply of materials, an increased number of health personnel, any clinical feedback to the midwives, optimization of the cleaning routines, and the introduction of a local flow chart (Annex II). The effects are not fully understood and new concepts are needed to evaluate them.[228] A brief historical overlook of outcome data from the Mulago National Referral Hospital indicated a decrease in mortality rates during the trial affecting both arms. The introduction of new tools may also favour them as study participants and health personnel may feel that they are better than the standard of care already in use. This may have affected both the evaluation of NeoTapLS and the introduction of the uncuffed LMA.

7.10 Emergency research

As previously described, we agreed on a 2-tiered consent procedure for the *NeoSupra Trial,* a prior brief oral consent, with deferred consent on Day 1 after birth. Cases of very early neonatal deaths was a challenge to the RAs since approaching distressed caregivers for deferred consent could be stressful and ethically difficult to justify. The inclusion of these participants was of utmost importance to the trial as death as an outcome was one of our primary concerns in the trial; there was inherently a risk that families losing a neonate would more likely drop out of the trial. This risk may have been especially high if the neonate was treated with the new device, LMA, since parents may be suspicious of new treatment protocols. After discussions with the RAs, we held on to the prior oral consent and deferred consents, even though informed consent would have been better in those particular cases. The benefit of not distressing all mothers entering the labour ward with extensive information on neonates needing PPV made this procedure best fitted to the context. The approach was successful and only a few mothers declined to give deferred consent.

The deep involvement of MHREC in the decisions on how to address the consent issue in our trial was essential for the trial. The procedure of consent in the

NeoSupra Trial was well suited for this context, but ethical guidelines for emergency resuscitation research need to be improved.

7.11 The impact of a pandemic on neonatal mortality

The data collection of this thesis was finalized before the outbreak of the latest pandemic due to coronavirus disease 2019, Covid-19. Logistically, it would have been difficult for me to undertake any observational studies and the *NeoSupra Trial* in Uganda during a pandemic. However, this thesis has been written during the pandemic; it feels right to mention any impact a pandemic may have had on neonatal mortality. The pandemic has disrupted many of the efforts taken towards the Every Newborn Action Plan and the SDG 3.2.[54,229,230] Until the end of 2019, advances in many areas of health continued, but the rate of progress was insufficient to meet most SDG 3.2 targets. Essential health services and lifesaving interventions are now being disrupted, which threatens to reverse decades of improvements in health outcomes. Increase in stillbirths and neonatal mortality have been reported.[231-233] One study provided evidence of the indirect effect of lockdowns in reducing institutional childbirth, as well as increasing the stillbirth rate and neonatal mortality.[231] Reasons might include reduced intrapartum care, lack of supplies, decreased number of staff and delay in transports.[234]

The pandemic will almost certainly have a negative effect on the progress towards the Every Newborn Action Plan and SDG 3.2, and will reduce research opportunities in low-resource settings. This will also have a negative effect on the implementation of innovations and new strategies and may be especially negative for neonates in low-resource settings.

8 Conclusion

This thesis extends our knowledge on innovations and new strategies, smartphone- and laryngeal mask airway use in cases where neonates are in need of positive pressure ventilation. More specifically:

- A smartphone app can accurately and rapidly assist in assessing a simulated heart rate and pulse on a manikin and a metronome rhythm
- Smartphone-assisted heart rate assessment by doctors is accurate and rapid in neonates not needing positive pressure ventilation in a low-resource setting
- Smartphone-assisted heart rate assessment by midwives was less accurate in neonates needing positive pressure ventilation in a low-resource setting
- The use of a laryngeal mask airway did not reduce early neonatal death or moderate-to-severe hypoxic-ischemic encephalopathy in asphyxiated neonates compared to face mask use
- Laryngeal mask airway use proved safe in the hands of midwives and can be an alternative device during neonatal resuscitation

9 Implications and future perspectives

9.1 Implications for policy

Midwives are the workforce primarily involved in saving neonates in low-resource settings, in which the majority of neonatal deaths occur. There is no single bullet solving the issue of neonatal mortality; midwives need our full attention if we are to reach the SDG 3.2 goal. To lower neonatal mortality, health systems need to be enforced at several levels, and innovations and new strategies need to be implemented where found useful and cost-effective. According to current guidelines, heart rate should be determined by auscultation or electrocardiography, and laryngeal mask airways should be used as an alternative device if face-mask ventilation is unsuccessful or endotracheal intubation is unavailable. The articles of this thesis add data supporting that:

- Heart rate assessment of neonates by auscultation with support from a smartphone is fast and accurate when carried out by doctors
- Helping Babies Breathe and other resuscitation training programs need to include auscultation-focused training in the curricula
- Task-shifting of airway access to midwives, including training with advanced manikins, the technique of laryngeal mask airway insertion, and video filming need to be considered, especially at the referral level in low-resource settings
- Midwives use the laryngeal mask airways safely
- Laryngeal mask airways can be used by midwives as a secondary device according to current guidelines
- WHO should consider adding laryngeal mask airway to the list of priority medical devices for essential reproductive, maternal, neonatal and child health
- A cost-analysis of laryngeal mask airway use is necessary, since both single-use and reusable models remain expensive

9.2 Implications for further research

Based on our experience, we strongly advise any future studies or trials in the field of neonatal resuscitation to use:

- Video-recording
- Dry-electrode electrocardiography

Our studies left some unanswered questions:

- How can smartphone apps best be used in training, teaching and clinical practice, both in small and large health facilities in low-resource settings? Clinical trials comparing smartphone-assisted HR estimations to dry-electrode electrocardiography could provide more data before clinical use
- Is task-shifting of heart rate assessment to non-doctoral health personnel feasible in low-resource settings?
- Can midwives be adequately trained to take over the responsibility of advanced resuscitation in low-resource settings?
- Can a new curriculum for high-volume referral hospitals in low-resource settings affect neonatal mortality and morbidity?
- Can laryngeal mask airway use affect mortality and morbidity in populations with less sick neonates? More detailed assessment of the outcome using electrocardiography and neuroimaging combined with Thompson scoring can clarify the results
- Can laryngeal mask airway use decrease the need for endotracheal intubation?
- Are mucus plugs causing airway obstruction during neonatal resuscitation more common in low-resource settings, and does aggressive suction solve the airway problem?
- How do consent procedures and medical care offerings affect the decision to participate in emergency medicine research?

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REGULAR ARTICLE

Accurate and fast neonatal heart rate assessment with a smartphone-based application – a manikin study

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ABSTRACT

Aim: This study determined the accuracy and speed of the NeoTapLifeSupport (NeoTapLS), a free smartphone application that aims to assess a neonate's heart rate.

Methods: We asked 30 participants with a variety of backgrounds to test the NeoTapLS, which was developed by our own nonprofit organisation Tap4Life, to determine a randomly selected heart rate by auscultation or palpation. The study was carried out in 2014 at Sachs' Children and Youth Hospital, Sweden, using a Laerdal SimNewB manikin that simulates true values. The NeoTapLS calculates the heart rate based on the user's last three taps on the smartphone screen.

Results: A total of 1200 measurements were carried out. A high correlation was found between measured and true values by auscultation (correlation coefficient 0.993) as well as by palpation (correlation coefficient 0.986) with 93.5% of the auscultations and 86.3% of the palpations differing from the true value by five beats or fewer. The mean time to the first estimated heart rate was 14.9 seconds for auscultation and 16.3 seconds for palpation.

Conclusion: Heart rates could be accurately and rapidly assessed using the NeoTapLS on a manikin. A globally accessible mobile health system could offer a low-cost alternative to expensive medical equipment.

INTRODUCTION

Intrapartum-related complications, labelled as birth asphyxia, account for up to 0.66 million deaths per year (1). Successful resuscitation could prevent a large proportion of early neonatal deaths, defined as death during the first seven days of life, and improve the number of neonates surviving asphyxia (2,3). In many low- and middle-income countries, neonatal resuscitation is frequently performed by health personnel with limited experience of airway management and a lack of reliable monitoring equipment. To improve the outcomes of delivery in these settings, all birth attendants, including physicians, midwives and nurses, should have the knowledge, tools and skills required to perform proper neonatal resuscitation.

The Helping Babies Breathe curriculum aims to implement basic skills in newborn resuscitation in resource-limited settings (4,5). The cornerstone of this training is to teach appropriate ventilation. An accurate assessment of heart rate provides further essential feedback on the quality of ventilation and is an important clinical indicator (6). Heart rate assessment is part of the Helping Babies Breathe training and flow chart, and it can be determined by auscultating the precordium or palpating the umbilical cord. Improved ventilation and further assistance are recommended if the heart rate is slow, defined as <100 beats per minute. Further heart rate assessment and advanced resuscitation is recommended if no improvements in heart rate and breathing are seen after improved ventilation.

Both the assessment of simulated heart rate on a manikin and the clinical assessment of heart rate in the delivery

Abbreviations
CI, Confidence interval; ECG, Electrocardiography; ILCOR, International Liaison Committee on Resuscitation; NeoTapLS, NeoTapLifeSupport; r, Correlation coefficient.

Key notes

- We asked 30 participants to test the NeoTapLifeSupport (NeoTapLS), a free smartphone application that aims to assess a neonate's heart rate.
- A total of 1200 measurements were carried out, and 93.5% of the auscultations and 86.3% of the palpations differed from the true value by five beats or fewer.
- The mean time to the first estimated heart rate was 14.9 seconds for auscultation and 16.3 seconds for palpation.

room are time-consuming, intermittent and often inaccurate (7,8). Electrocardiography (ECG) is fast and accurate, but is typically unavailable in resource-limited settings (9). Pulse oximetry displays both pulse and saturation. In neonatal resuscitation, the most important parameter is the pulse of the newborn infant. Using pulse oximetry to assess an infant's heart rate can identify, with high sensitivity and specificity, those infants who require interventions based on current recommendations, but the procedure is slow and is also often unavailable in resource-limited settings (10). In one simulation study, where study participants assessed heart rates by registering the heart rate tapped out by an examiner using his or her finger, the estimated heart rates showed little accuracy, especially at rates of <60 beats per minute (11). The need to develop a rapid and accurate method for determining heart rate during newborn resuscitation has been highlighted (12–14).

A systematic review, published in 2017, explored the accuracy of seven new technologies for monitoring the heart rates of newborn infants and compared them to current reference standards (13). The authors suggested that pairing digital stethoscopes with a smartphone might improve global assessments of heart rate, including resource-limited settings. However, they concluded that the seven new technologies tested could not be recommended as suitable for widespread clinical use at that stage (13).

The 2015 International Liaison Committee on Resuscitation (ILCOR) guidelines state that progress beyond the initial steps of newborn care, namely position of the airway, suction if needed, drying and stimulation, is determined by the simultaneous assessment of two vital characteristics: respiration and a heart rate of <100 beats per minute. Furthermore, chest compressions should be initiated if the heart rate is <60 beats per minute, after having ensured that the patient has adequate ventilation. ILCOR suggest that an ECG should be used to evaluate heart rates in newborn infants who need resuscitation, but an ECG does not replace the need for pulse oximetry to evaluate the newborn infant's oxygenation (15). Compared to the 2010 ILCOR guidelines, the new guidelines place less emphasis on auscultation (6,15). However, when ECG and pulse oximetry are not available, auscultation is still recommended. The current ILCOR guidelines do not provide other alternative heart rate monitoring methods. Given that a great majority of neonatal deaths occur in resource-limited settings, there is an urgent need for a reliable, inexpensive and readily available tool to assess heart rates under these conditions.

NeoTapLifeSupport (NeoTapLS) is a new free-of-charge smartphone application that is designed to evaluate neonatal heart rates and was developed by our own nonprofit organisation (Tap4Life, Stockholm, Sweden). The development of this application responded to the demand identified in our previous study for a method to assess the heart rate of newborn infants in a fast and accurate way in a resource-limited setting where no other reliable monitoring equipment was available (16).

The user listens to the heart beat, or feels the pulse, of the newborn infant and then taps the pace of the heart rate at least three times on the screen of the smartphone. The NeoTapLS then displays the heart rate as a number on the screen. The interface is designed to be visible and functional even when the smartphone is placed in a latex glove for protection, which is useful in healthcare service in resource-limited settings. The heart rate is also colour-coded: red for a heart rate of <60, yellow for a heart rate of 60–99 and green for a heart rate of 100 or more. The NeoTapLS is downloadable free of charge at Google Play.

The aim of this manikin study was to determine the accuracy and speed when participants with a range of professional and educational backgrounds assessed a simulated heart rate using the NeoTapLS.

METHODS

Study participants

This observational study was conducted in 2014 at the Centre for Education in Paediatric Simulation at Sachs' Children and Youth Hospital in Stockholm, Sweden. It tested the NeoTapLS, a new free-of-charge android application. To cover a wide range of clinical resuscitation skills, we recruited participants who were unfamiliar with the NeoTapLS and came from a variety of professional and educational backgrounds. All the people we approached agreed to take part in the study, and any prior experience in smartphone management was disregarded. We included 30 participants: eight doctors, six nurses, three nurse assistants, six nurse students, two medical students, three secretaries and two web designers.

The simulated heart rate, auscultated over the precordium or palpated by the pulse, was simultaneously tapped onto the smartphone screen. After three taps, a colour-coded number indicating the heart rate was displayed (Fig. 1).

A neonatal patient simulator, the Laerdal SimNewB manikin (Laerdal Medical, Stavanger, Norway), was used for the tests. This manikin is capable of generating heart tones as well as umbilical and brachial pulsations. Before starting the simulation, 20 heart rates, within the range of 20–140, were chosen using a random number generator (17). As the manikin could only present in multiples of tens, the numbers from the random number generator were rounded to the nearest ten. The 20 heart rates were presented to the participants in two orders, one for auscultation and one for palpation. Participants were not informed that the manikin could only present numbers in tens. The participants were blinded to the selected heart rates.

All users were introduced to the NeoTapLS and the Laerdal SimNewB, and they familiarised themselves with the set-up for three to five minutes prior to the simulation. They were instructed to determine the heart rate by auscultation of the precordium or palpation of the brachial pulse of the Laerdal SimNewB manikin and simultaneously tap the same pace on the screen of a smartphone, with the NeoTapLS app installed. The simulation began by the researcher telling the participants to start. As soon as

Figure 1 (A, B, C) How the NeoTapLS is displayed on the smartphone screen. Tap to register the infant's heart rate. (A) Heart rate at 32 seconds <100, prepare for ventilation. (B) Heart rate at one minute <100, ventilate now! (C) Heart rate at one minute 45 seconds >100, newborn resuscitation is going well.

the participants were sure of the heart rate, they said stop and reported the number. The acquisition time, defined as the time from start to stop, was noted for all scenarios. Each of the 30 participants carried out 20 estimations for auscultation and 20 for palpation of the brachial pulse of the Laerdal SimNewB, resulting in a total of 1200 readings. Auscultation of the precordium was performed using a 3M Littman Classic II Infant Stethoscope (3M, Minnesota, USA). In all scenarios, the Laerdal SimNewB manikin was lying on an open resuscitation table, without respiratory frequency (Fig. 2).

Sachs' Children and Youth Hospital, Stockholm, Sweden, approved the study. Further ethical approval was not considered necessary for this study as it focused on the accuracy and speed of the method and not on comparing performance between individual participants or groups of participants, similar to a previously published manikin study (18). The participants gave oral consent to participate and could decline participation at any time during the study.

Statistical analysis

The analyses were performed using Stata Statistical Software version 14.0 (StataCorp LP, College Station, Texas, USA). Numerical variables were summarised with means, ranges and standard deviations, and categorical variables were summarised using frequencies. To compare correlations between numerical variables, Pearson correlation coefficients (r) were estimated. Results were presented with 95% confidence intervals (CI). All the inferential analyses were adjusted to take into account the clustered nature of the data, as the data clustered within individuals. P values of <0.05 were considered significant.

RESULTS

The estimated heart rates were arranged into three categories: very low (<60), low (60–99) or normal (≥100). The simulated heart rates were categorised into very low (20–50), low (60–90) or normal (100–140). The heart rate of the manikin, which was equal to the true value, will henceforth be called the simulated heart rate.

Auscultation

The correlation between the estimated and simulated heart rates was high (r = 0.993). It was lower in the normal range (r = 0.920) compared to the very low (r = 0.974) and low range (r = 0.974). Overall, 93.5% of all auscultations differed by five beats or less from the true value (Fig. 3).

In all, 18/600 (3.0%) estimations of simulated heart rate by the 30 participants were placed in a category that was different to the actual category of the simulated heart rate

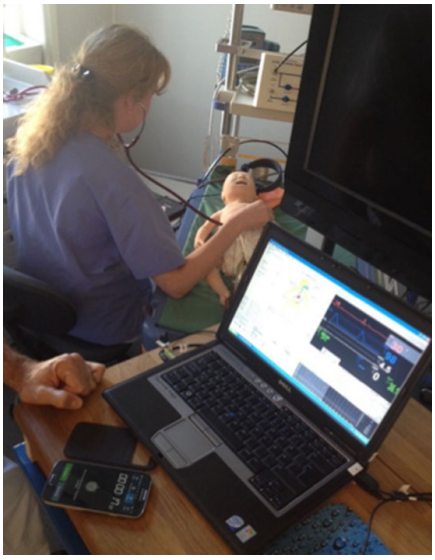

Figure 2 A simulation in which a participant, who agreed to be photographed, auscultated the precordium of the manikin and at the same time tapped the screen of the smartphone with the NeoTapLS application.

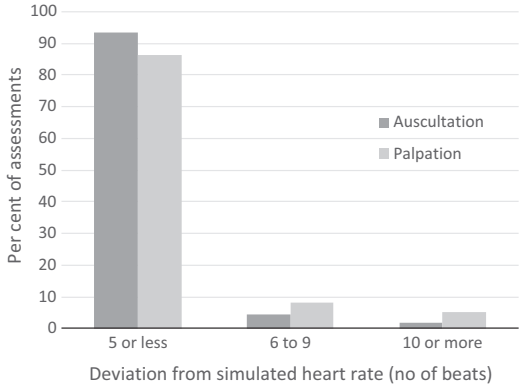

Figure 3 Deviation from simulated heart rate by auscultation and palpation.

(Table 1). In the very low range, none were misclassified. Misclassifications were more likely to happen in the estimations of simulated heart rates at 60 and 100 as they were cut-offs for the three categories. We found that 2/30 were misclassified at 60 and 1/30 differed by five beats or less from the simulated heart rate 60. Furthermore, 15/90 were misclassified at 100 and 12/90 differed by five beats or less from the simulated heart rate of 100. If the 120 simulated heart rates of 60 and 100 were excluded, because just a difference of one beat could lead to the wrong categorisation, only one of the 480 (0.2%) estimations was misclassified.

The mean difference between the estimated and simulated heart rate was 0.79 beats per minute (95% CI −0.11 to 1.68). There was a slight, but constant, overestimation, and this occurred more frequently in the normal range than in the lower ranges. In the very low range, it was 0.39 beats per minute (95% CI −0.03 to 0.81); in the low range, it was 0.68 beats per minute (95% CI 0.07 to 1.28); and in the normal range, it was 1.14 beats per minute (95% CI −0.73 to 3.02). The prevalence of correct estimations increased in a similar way from the normal range to the very low range (p value < 0.001) (Fig. 4A).

The mean acquisition time for the estimated heart rate was 14.9 seconds (95% CI 13.42 to 16.40), ranging from two to 80 seconds. The mean acquisition time was longer in the very low range at 17.8 seconds (95% CI 16.5 to 19.2), compared to 13.1 seconds in the low range (95% CI 11.5 to 14.6) and 13.4 seconds in the normal range (95% CI 11.6 to 15.3) (p value < 0.001).

Palpation

The correlation between the estimated and the simulated heart rate for palpitation was high (r = 0.986), as it was for auscultation. The correlation was highest in the very low range (r = 0.956) and lower in the low range (r = 0.906). The normal range had the lowest correlation (r = 0.840). Overall, 86.3% of all palpations differed by five beats or less from true value (Fig. 3).

In all, 39/600 (6.5%) estimations of simulated heart rate by the 30 participants were placed in a category that was different to the actual category of the simulated heart rate (Table 1). We found that 7/30 were misclassified at 60 and 6/30 differed by five beats or less from the simulated heart rate of 60. Furthermore, 23/90 were misclassified at 100 and 18/90 differed by five beats or less from the simulated heart rate of 100. If the 120 simulated heart rates of 60 and 100 were excluded, again because just a difference of one beat could lead to the wrong categorisation, 9/480 (1.9%) estimations were misclassified.

The mean difference between the estimated and simulated heart rate was −0.02 beats per minute (95% CI −1.08 to 1.04). In the very low range, it was 0.68 beats per minute (95% CI 0.20 to 1.16); in the low range, it was −0.29 beats per minute (95% CI −1.61 to 1.03); and in the normal range, it was −0.44 beats per minute (95% CI −2.21 to 1.36). The estimated heart rates were not significantly lower or higher than the simulated heart rates (p value 0.94), meaning that there was no consistent over- or underestimation (Fig. 4B).

The mean acquisition time for the estimated heart rate was slightly longer than for auscultation, at 16.3 seconds (95% CI 14.7 to 17.9), and it ranged from 5 to 62 seconds. The mean acquisition time was 18.7 seconds in the very low range (95% CI 17.3 to 20.1), 14.6 seconds in the low range (95% CI 12.9 to 16.2) and 15.1 seconds in the normal range (95% CI: 13.1;17.1) (p value < 0.001).

Table 1 Estimated heart rate and simulated heart rate by auscultation and palpation, divided by categories, according to the 2015 ILCOR guidelines

		Very low simulated heart rate 20–50 N = 210 n (%)	Low simulated heart rate 60–90 N = 120 n (%)	Normal simulated heart rate 100–140 N = 270 n (%)
Estimated heart rate <60	By auscultation	210 (100)	2 (1.7)	0 (0)
	By palpation	209 (99.5)	8 (6.7)	0 (0)
Estimated heart rate 60–99	By auscultation	0 (0)	117 (97.5)	15 (5.6)
	By palpation	1 (0.5)	111 (92.5)	29 (10.7)
Estimated heart rate 100 or higher	By auscultation	0 (0)	1 (0.8)	255 (94.4)
	By palpation	0 (0)	1 (0.8)	241 (89.3)

DISCUSSION

This study showed that assessment of a simulated heart rate in a manikin using a newly developed application for smartphones, the NeoTapLS, was fast and accurate. Overall, 93.5% of the assessments made by auscultations and 86.3% of the assessments made by palpations differed by five beats or less from the heart rate simulated by the manikin.

Prior to our study, auscultation and palpation had repeatedly been shown to lead to incorrect management, even in manikin studies. One study found that up to 28% of simulated heart rates obtained by auscultation led to incorrect management (7), while another reported that heart rates below 60 beats per minute were inaccurate and overestimated simulated heart rate (11). A third study stated that errors in initial heart rate determination occurred in 26–48% of the time (19). A clinical study reported poor agreement between the assessments of heart rate in newborn infants when both auscultation and palpation were used (20). In healthy newborn infants, brachial and femoral pulses are not reliable for determining heart rates (19,20) and umbilical pulsations must not be relied upon whether they are low or absent (20). Two reviews have pointed out problems with the inaccuracy of existing methods (13,14).

In contrast, our study showed that very few heart rate estimations fell on the wrong side of the cut-off levels at 100 beats per minute (2.7% of auscultations and 5.0% of palpations) and 60 beats per minute (0.3% of auscultations and 1.5% of palpations). If simulated heart rates of 60 and 100 were excluded, because just a difference of one beat could lead to the wrong categorisation, an even smaller number would be misclassified (0.2% of auscultations and 1.9% of palpations).

As 93.5% of the NeoTapLS-assisted auscultations and 86.3% of the NeoTapLS-assisted palpations differed by five beats or less from the true value, it is unlikely that the results would lead to major differences in the management of cardiopulmonary resuscitations. A heart rate of 100 is the cut-off for the definition of normal heart rate and guides the resuscitator to re-evaluate ventilation and <60 is the cut-off for initiating heart compression, according to the ILCOR guidelines. This means that incorrect estimations when the heart rate is near these cut-off points could eventually lead to wrong assumptions about the status of the newborn infant. Our findings are encouraging and may prevent incorrect management in the resuscitation of newborn infants (15).

Time is an extremely important factor in neonatal resuscitation. ECG monitoring in the delivery room can be time-consuming (8) and may be difficult to apply due to the infant's wet skin. Pulse oximetry is also time-consuming, it needs an extra pair of hands, and it is often unreliable in the delivery room, because it is sensitive to the excessive motion and low blood perfusion displayed by newborn infants. One study showed that it took a median of 68 seconds to obtain a heart rate by pulse oximetry (10). Another study showed that the time interval from attaching the pulse oximetry unit to the first heart rate value appearing on the monitor was 84 seconds (range 35–132 seconds) (21). In fact, neither ECG nor a conventional pulse oximetry is fast enough to enable delivery room staff to follow the international resuscitation guidelines for newborn infants. In our study, simulated heart rate assessment was possible within one minute, with few exceptions, and in most of the assessments, it took <20 seconds. This means that, at least under simulation conditions, it is possible to use the heart rate information to guide the management of the infant.

Furthermore, both ECGs and pulse oximetry are expensive and are rarely available in resource-limited settings. With the number of mobile phone users in the world expected to pass the five billion mark in 2019, wireless technology is expanding even in the most remote parts of the world (22). The widespread use of mobile phones highlights a significant opportunity to have a global impact on health behaviours (23). Low-cost smartphones are readily available and used at the patient's bedside by an increasing number of health workers (23). Free-of-charge mobile health tools, like NeoTapLS, can be available for all health workers who have access to a smartphone. In addition, the smartphone can easily be protected by a glove.

A manikin study is close to an ideal situation for assessing heart rate, or, in fact, simulated heart rate. There is little stress, no interfering sounds, no dirt and none of the movement seen in a real newborn infant. This is a limitation of any manikin study (7). However, a manikin study can be used to prove a concept that can then be tested further in

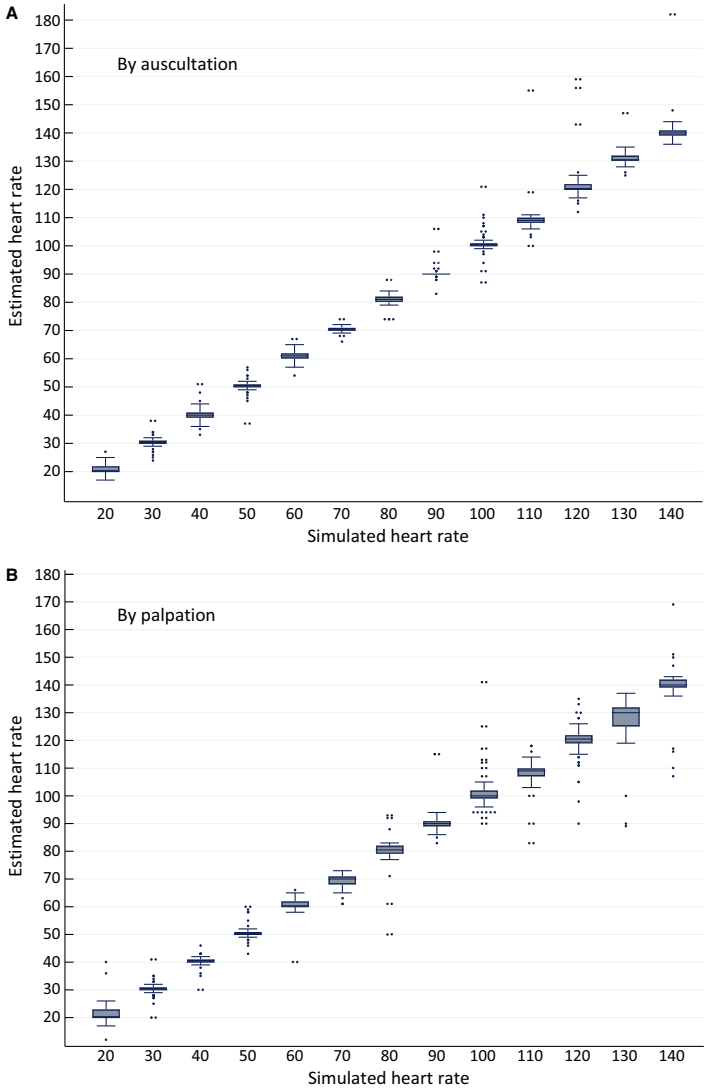

Figure 4 (A, B) Boxplot and whiskers showing all estimated heart rate assessments with NeoTapLS versus simulated heart rate of the manikin (A) by auscultation and (B) by palpation.

clinical environments. The manikin we used, the Laerdal SimNewB, could only present numbers in multiples of 10, but as the participants were not aware of this, it should not have affected the results. Furthermore, as the 30 participants were from a number of different professions, and the results were accurate, swift and significant for the entire group, the results indicate that the application is user-friendly and that it is possible to learn the required method with just a few minutes training.

The results from our study are encouraging and suggest that healthcare staff could avoid erroneous and delayed estimations of heart rate if they used the NeoTapLS in clinical practice. Our results also indicate that auscultation, with a stethoscope over the precordium of the newborn, should be a preferred method to palpation. In the absence of a stethoscope, palpation combined with NeoTapLS may be an alternative method for accurately and quickly assessing the heart rate. The NeoTapLS could also be used as a backup if

monitoring equipment fails or in the absence of any other equipment. The ILCOR guidelines advocate auscultation for initial heart rate assessment and ECG or pulse oximetry if the baby needs neonatal resuscitation and/or continuous respiratory support. The ILCOR does not provide recommendations for other alternative methods of evaluating heart rates, when expensive medical devices are unavailable. Mobile health tools such as the NeoTapLS could fill this gap.

CONCLUSION

Our study showed that heart rates were accurately and rapidly assessed using the NeoTapLS on a manikin. The operators can start the NeoTapLS at the time of birth, and it keeps track of the time and reminds them to start ventilation at 60 seconds. NeoTapLS makes it possible to evaluate the heart rate with a minimum interruption of ventilation, even when only one resuscitator is in attendance. A globally accessible mobile health system offers a low-cost alternative to expensive medical equipment. Future studies, including clinical trials that compare smartphone-assisted heart rate estimations to ECG or pulse oximetry, could provide more data on the potential of NeoTapLS prior to clinical use.

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CONFLICT OF INTERESTS

Four of the five authors are cofounders of the nonprofit organisation Tap4Life, which produces the free-of-charge NeoTapLS application.

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II

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Smartphone app for neonatal heart rate assessment: an observational study

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ABSTRACT

Background Heart rate (HR) assessment is crucial in neonatal resuscitation, but pulse oximetry (PO) and electrocardiography (ECG) are rarely accessible in low-resource to middle-resource settings. This study evaluated a free-of-charge smartphone application, NeoTap, which records HR with a screen-tapping method bypassing mental arithmetic calculations.

Methods This observational study was carried out during three time periods between May 2015 and January 2019 in Uganda in three phases. In phase 1, a metronome rate (n=180) was recorded by low-end users (midwives) using NeoTap. In phase 2, HR (n=69) in breathing neonates was recorded by high-end users (paediatricians) using NeoTap versus PO. In phase 3, HR (n=235) in non-breathing neonates was recorded by low-end users using NeoTap versus ECG.

Results In high-end users the mean difference was 3 beats per minute (bpm) higher with NeoTap versus PO (95% agreement limits −14 to 19 bpm), with acquisition time of 5 seconds. In low-end users, the mean difference was 6 bpm lower with NeoTap versus metronome (95% agreement limits −26 to 14 bpm) and 3 bpm higher with NeoTap versus ECG in non-breathing neonates (95% agreement limits −48 to 53 bpm), with acquisition time of 2.7 seconds. The agreement between NeoTap and ECG was good in the HR categories of 60–99 bpm and ≥100 bpm; HR <60 bpm had few measurements (kappa index 0.71, 95% CI 0.63 to 0.79).

Conclusion HR could be accurately and rapidly assessed using a smartphone application in breathing neonates in a low-resource setting. Clinical assessment by low-end users was less accurate with wider CI but still adds clinically important information in non-breathing neonates. The authors suggest low-end users may benefit from auscultation-focused training. More research is needed to evaluate its feasibility in clinical use.

What is known about the subject?

- Heart rate is crucial in evaluating the status of neonates during resuscitation.
- Previous simulation studies and an animal model have shown that a smartphone application, NeoTap, offers fast and accurate heart rate monitoring.
- Clinical data on heart rate monitoring of neonates with a smartphone app are not yet available.

What this study adds?

- A smartphone application can improve speed and accuracy during heart rate assessment of neonates by auscultation in clinical setting.
- NeoTap could be a low-cost alternative to expensive medical equipment in both low-resource and high-resource settings.

INTRODUCTION

Neonatal deaths stand at 47% of all deaths in children <5 years of age, equal to 2.5 million neonates dying in 2017, with about 1 million dying on the first day.[1 2] Intrapartum-related events (birth asphyxia) stand at around 0.66 million deaths (uncertainty range of 0.42–1.05 million).[3] Moreover, 2.6 million stillbirths occur every year, 50% after the onset of labour.[4] Successful resuscitation could prevent many early neonatal deaths and decrease the morbidity of neonates surviving asphyxia.[5]

Heart rate (HR) is one of the most important clinical parameters in evaluating the status of a neonate, to guide neonatal resuscitation and to predict early neonatal mortality and morbidity.[6–8] International guidelines state that resuscitation efforts should be guided by checking respiration and HR.[7 9] Pulse oximetry (PO) is valuable in monitoring HR and measuring oxygen saturation,[10 11] but HR is measured faster and more accurately through electrocardiography (ECG).[7 9] Auscultation, recommended when PO and ECG are unavailable, is often inaccurate.[12–16] Doppler is not recommended in current international guidelines.[7 9] Resource-limited settings rarely have PO, ECG or Doppler.[17] In 2017, a systematic review investigated the accuracy of seven new technologies for monitoring HRs of neonates and concluded that none could be recommended as suitable for widespread clinical use at this stage.[18] The need to develop a low-cost, rapid and accurate alternative method for

Figure 1 Tap to record the neonate's heart rate by the NeoTap application. Heart rate <100 bpm (yellow) at 37 s: prepare for ventilation. Heart rate <60 bpm (red) at 2 min and 11 s: start chest compressions? Heart rate ≥100 bpm (green) at 3 min and 37 s: neonatal resuscitation is going well. bpm, beats per minute.

monitoring HR during neonatal resuscitation has been highlighted.[18 19]

NeoTap (NeoTap Life Support-NeoTapLS) is a free-of-charge smartphone app for HR recording (Google Play and App Store), developed by a non-profit organisation (Tap4Life, Stockholm, Sweden).[20 21] It uses a screen-tapping method; the user auscultates the heart sounds and taps the beat on the screen a minimum of three times, and the app generates a number, bypassing mental arithmetic (figure 1). No probes are needed, and the interface is functional even when protected inside a latex glove. The app can also be used to estimate cord pulsations and fetal HR; an instructional video on 'How to use NeoTapLS' is available in online supplementary file 2 and the full version is available on YouTube. A significant proportion of health personnel in low-resource settings have their own smartphone, a number that is increasing.[22] NeoTap has shown promising results from three simulation studies and an animal model.[23–26]

The aim of our study was to evaluate NeoTap by determining the speed and accuracy at which users could assess a rhythm by a metronome (low-end users, midwives well familiar with neonatal resuscitation but with no prior experience of the tapping method), HR in breathing neonates (high-end users, paediatricians well familiar with the tapping method), and HR in neonates in need of positive pressure ventilation (PPV), equal to neonates with insufficient or no breathing at birth (low-end users). The hypothesis was that NeoTap is as fast or faster than PO and ECG and accurate enough to guide neonatal resuscitations.

METHODS

Study design

This prospective observational study was carried out during three time periods between May 2015 and January 2019. It is a substudy of the 'Randomized Clinical Trial Assessing Laryngeal Mask Airway Versus Face-Mask Ventilation in Neonatal Resuscitation (LMA vs FMV)' (ClinicalTrials.gov NCT02042118) and the 'Neonatal Resuscitation with Supraglottic Airway Trial (NeoSupra)' (ClinicalTrials.gov NCT03133572), conducted at the Department of Obstetrics and Gynaecology, Mulago National Referral Hospital, Uganda, which has around 25 000 deliveries per year.

Data collection

The study had three phases to evaluate NeoTap by testing low-end users' ability to tap a metronome rhythm and high-end and low-end users' ability to tap a correct HR in clinical practice, as well as assess the swiftness of the method in clinical use. Low-end users in the first and third phases were research midwives and exposed on a daily

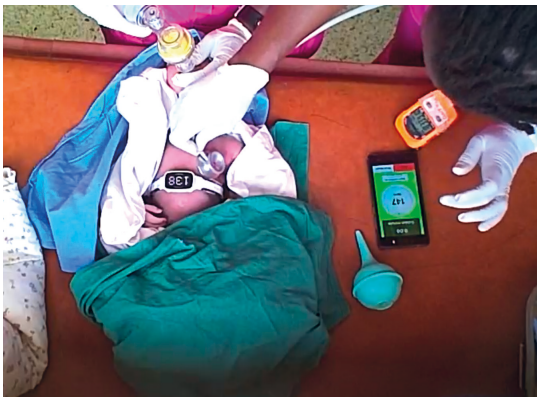

Figure 2 Low-end user using NeoTap to record heart rate (heart rate shown 147) and dry-electrode electrocardiography (heart rate shown 138). Picture used with written permission from the parents.

basis to neonatal resuscitation and trained according to Helping Babies Breathe, as part of the NeoSupra trial.[27] High-end users were two paediatric specialists. The users simultaneously tapped the pace of the rhythm of the metronome, or the HR they auscultated over the heart of the neonate, on the smartphone screen with the NeoTap app running. NeoTap is designed to display the average rate of the last three taps, meaning a number was displayed after a minimum of three taps (figure 2). The metronome was used as the true value in phase 1, HR by PO (PalmSAT 2500, Nonin Medical, Plymouth, USA) as the true value in phase 2 (no other monitoring equipment was available at the time), and HR by ECG as the true value in phase 3. A convenience sample was chosen for each phase due to practical reasons and the exploratory nature of the study.

Phase 1: metronome rate by NeoTap (low-end users, a simulation)

In phase 1 we assessed the ability of low-end users to correctly record an audible metronome rhythm. Ten rates were randomly selected using a number generator set over the range of 20–150 beats per minute (bpm),[28] and the rates (masked to the participants) were presented by the metronome for approximately 20 s. Low-end users recorded the rate with the NeoTap, after first being introduced to the app for 3–5 min, and wrote down the rate obtained on separate papers. The midwives included in the study were chosen irrespective of prior experience of smartphones. Informed consent was obtained from all participants.

Phase 2: HR by NeoTap versus PO (high-end users, healthy neonates)

In phase 2, we assessed the swiftness and ability of two high-end users to accurately record HR using NeoTap compared with PO in neonates not in need of PPV. PO was placed on the neonate on arrival on the resuscitation table by one high-end user and HR was assessed using NeoTap by the second high-end user as soon as HR was displayed by PO. Directly after HR was assessed using NeoTap, the second high-end user checked the HR on the PO (not masked to the participants) and noted both HRs on a paper. Acquisition time of NeoTap was noted (defined in seconds from start to end of tapping). Data were collected on-site when high-end users were available, and it was at this stage when it was unfeasible to involve low-end users since few were available. The first four paired HRs per neonate were collected. Informed consent was obtained from the parents on maternal admission and from the high-end users.

Phase 3: HR by NeoTap versus ECG (low-end users, neonates in need of PPV)

In phase 3, we assessed the swiftness and ability of low-end users to accurately record HR using NeoTap compared with ECG in neonates in need of PPV. ECG was placed on the neonate once feasible and HR was assessed using NeoTap when HR was displayed by ECG and compared with HR obtained by ECG at the same time (not masked to the participants). Low-end users were already introduced to NeoTap in phase 1 and did not receive additional training prior to phase 3. The acquisition time of NeoTap was noted as in phase 2. No high-end users were available at the study site, and it was therefore not possible to include them. All resuscitations were video-recorded using an HD 1080P Black Box AI-IP018 camera (Shenzhen Aishine Electronics, China). The first 49 HR data were supervised by the researchers and collected on-site by traditional ECG (Philips Intellivue X2, Amsterdam, The Netherlands), and the rest were unsupervised and collected from video review with dry-electrode ECG (NeoBeat, Laerdal Global Health, Stavanger, Norway). All paired HRs (HR by NeoTap at the same time as HR by ECG) until end of resuscitation were collected; no upper limit was set for numbers of assessments per neonate (figure 2). All neonates lacking simultaneous data (only one device, poor signal acquisition or poor camera angle) were excluded (n=270). Data on Apgar and weight were double-entered using Android devices running the Open Data Kit V.2.0 tool suite.[29] Written and oral information was given to all parents on maternal admission, and deferred consent was obtained post-hoc in cases needing resuscitation.[27]

Patient and public involvement

It was not appropriate to involve patients or the public in the design, or conduct, or reporting or dissemination plans for the study.

Data analysis

The agreement in phase 1 was assessed using a Bland-Altman plot (including Pearson's correlation coefficient between HR difference and HR values). The agreement in phase 2 and 3 was assessed using a Bland-Altman plot for repeated measures (including repeated measure correlation between HR difference and HR values), and

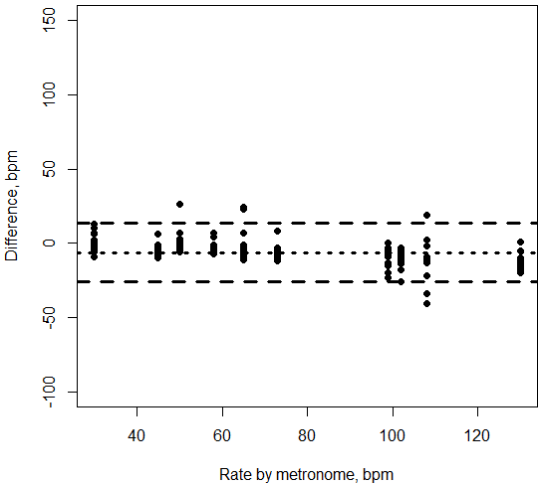

Figure 3 Agreement between the metronome rhythm and the rate low-end users recorded using NeoTap: a simulation. Metronome rhythm is shown on the x-axis and the difference from recordings done by NeoTap on the y-axis (Bland-Altman plot) (data set in online supplementary file). bpm, beats per minute.

in phase 3 using repeated measures version of kappa index on the following HR categories: <60, 60–99 and ≥100 bpm. The sensitivity and specificity of NeoTap in detecting bradycardia (HR <100 bpm) were also calculated. Acquisition times in phase 2 and 3 were summarised with median and IQR for descriptive purposes.

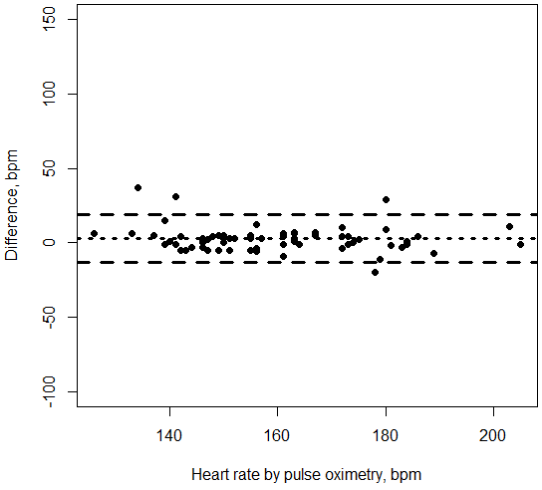

Figure 4 Agreement between NeoTap and pulse oximetry among high-end users recording heart rate in healthy breathing neonates. Pulse oximetry recording is shown on the x-axis and the difference between the readings on the y-axis (Bland-Altman plot) (data set in online supplementary file). bpm, beats per minute.

Table 1 Characteristics of neonates in phase 2 and 3 of the study

Characteristics	Phase 2	Phase 3
Number of neonates	33	98
Number of recordings	69	235
In need of PPV	No	Yes
Apgar 1 min	9 (IQR 9–9)	3 (IQR 2–4)
Apgar 5 min	9 (IQR 9–10)	5 (IQR 4–6)
Median weight (g)	3000 (IQR 2700–3390)	3100 (IQR 2750–3400)
Time of HR assessment after birth (s)	120–1800 (median 300, IQR 180–600)	~100–720*

*Exact data on time for measurements not possible to obtain through the method used in phase 3.
HR, heart rate; PPV, positive pressure ventilation.

Statistical analysis was performed using R V.3.5 (R Foundation for Statistical Computing, Vienna, Austria).[30]

RESULTS

During the three phases we had no issues with the reliability of the app. The app is designed to use very low resources from the phone and is continuously updated. It never crashed and froze and no battery problems occurred. The quality of the videos in phase 3 was excellent, with only a few exclusions due to non-visible HR on NeoTap or ECG.

Phase 1: metronome rate by NeoTap (low-end users, a simulation)

One hundred and eighty recordings were assessed by 18 low-end users. There was a mean difference of −6 bpm with NeoTap versus metronome, with 95% agreement limits of −26 to 14 bpm (Bland-Altman plot) (figure 3). The difference was inversely correlated with the metronome rhythm (r=−0.50, p<0.0001), moving from an overestimation to an underestimation. NeoTap recordings ranged from 21 to 131 bpm, and the metronome was set at a range of 30–130 bpm. In total 77% differed by 10 or less from the true value and 95% differed by 20 or less.

Phase 2: HR by NeoTap versus PO (high-end users, healthy neonates)

Sixty-nine HR recordings were assessed on 33 neonates as soon as HR by PO was available, which was at 120 s or more after birth (table 1). There was a mean difference of 3 bpm with NeoTap versus PO, with 95% agreement limits of −14 to 19 bpm (Bland-Altman plot) (figure 4). The difference was inversely correlated with HR (r=−0.43, p=0.009); it decreased, not towards a zero difference, but towards a negative difference. HR ranged from 132 to 214 bpm with NeoTap, and from 126 to 205 bpm with PO. The median acquisition time for the estimated HR was 5 s

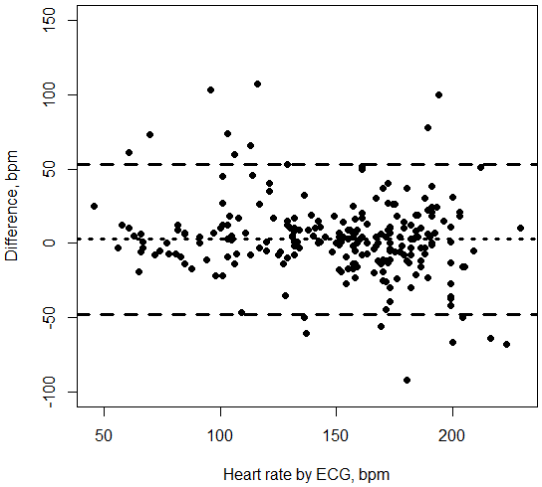

Figure 5 Agreement between NeoTap and ECG among low-end users recording heart rate in non-breathing neonates during neonatal resuscitation. ECG recordings are shown on the x-axis and the difference between the readings on the y-axis (Bland-Altman plot) (data set in online supplementary file). bpm, beats per minute; ECG, electrocardiography.

(IQR 5–5), ranging from 3 to 15 s. In total, 88% differed by 10 or less from the true value and 96% differed by 20 or less.

Phase 3: HR by NeoTap versus ECG (low-end users, neonates in need of PPV)

Two hundred and thirty-five HR recordings were assessed by approximately 18 low-end users on 98 neonates (table 1). There was a mean difference of 3 bpm with NeoTap versus ECG, with 95% agreement limits of −48 to 53 bpm, a difference that did not correlate with HR (r=−0.06, p=0.51) (Bland-Altman plot) (figure 5). HR ranged from 46 to 294 bpm with NeoTap, and from 46 to 229 bpm with ECG. The median acquisition time for the estimated HR was 2.7 s (IQR 1.7–4.7), ranging from 0.8 to 13.9 s. When HR was evaluated using the categories <60, 60–99 and ≥100 bpm (table 2), the agreement between NeoTap and ECG was good (kappa index 0.71, 95% CI 0.63 to 0.79). The <60 bpm category included only three recordings, with NeoTap differing +3, −12 and −25 from ECG. The 60–99 bpm category included 27 recordings differing by a median of 7 (IQR 5–14) from the true value, and the >100 bpm category included 205 recordings differing by a median of 12 (IQR 5–24) from the true value. In total, 48% differed 10 or less from the true value and 73% differed by 20 or less. Overall, NeoTap showed very good sensitivity (0.87) and specificity (0.96) in detecting bradycardia (HR <100 bpm).

The complete data set for all three phases is available in online supplementary file.

Table 2 Distribution in categories of correctly and incorrectly recorded heart rates among midwives assessing neonates in need of positive pressure ventilation compared with electrocardiography, phase 3

NeoTap	Electrocardiography		
	<60 bpm	60–99 bpm	≥100 bpm
<60 bpm	1	1	0
60–99 bpm	2	22	8
≥100 bpm	0	4	197

Data expressed as number of evaluations in each category.
bpm, beats per minute.

DISCUSSION

This study presents new data on the feasibility of using a smartphone app for swift and accurate HR assessments in neonates, both those in need and not in need of PPV. NeoTap showed variable accuracy and precision in estimating rates and HRs, especially in low-end users in HR auscultation. Low-end users could quickly learn the tapping technique and both high-end and low-end users were quick in estimating HRs.

In low-resource settings, neonatal resuscitation is mainly carried out by health personnel with limited experience in both airway management and auscultation. Reliable monitoring equipment is rarely available.[17] HR assessment is inaccurate due to imprecise auscultation and palpation or errors in mental arithmetic calculation.[12–16 31] Auscultation is a three-step procedure: first is auscultating the heart, second is understanding what you hear (first and second heart sounds) and third is translating it by calculation to provide a number. A recent clinical study showed that HR auscultation by clinicians compared with PO and ECG was quick and reasonably accurate in neonates not in need of PPV. Still, studies during neonatal resuscitation with less experienced health personnel are lacking.[32] Although imprecise, international guidelines recommend HR determination by physical examination if no PO and/or ECG are available.[7 9]

NeoTap over-rides the need for mental arithmetic calculations. In 2018, two simulation studies reported that HR could be accurately and rapidly assessed using NeoTap on a manikin.[23 24] In 2019, another simulation study showed that NeoTap reduced the time to the first HR and the time to initiate heart compressions and to administer epinephrine compared with auscultation and mental computation.[25] A porcine model showed that HR assessment with NeoTap had similar accuracy compared with auscultation with a digital stethoscope, ECG or carotid blood flow during asphyxia and faster acquisition time compared with the 6 s or 10 s method with a digital stethoscope.[26] However, data on the clinically important group of HR <60 bpm are few and show contradictory results in the studies above as well as in the present study. A recent review on HR assessment stated that novel technologies including tap-based applications can support

HR assessment, but that their clinical efficacy during neonatal resuscitation has yet to be investigated.[33]

The accuracy in this study was highest among low-end users recording a metronome rhythm and in high-end users recording HR compared with PO in neonates not in need of PPV. In phase 1 there was an inverse correlation between the bpm presented and the difference—participants overestimate low beats and underestimate high beats. We think this is because in low rates it is easy to tap too early and be too eager to tap the screen even when no sounds are presented, and in high rates it is hard to keep the high speed if you are not used to the tapping technic. In clinical use, this effect may be problematic in low HRs, but in high HRs it has minor clinical implications. Low-end users demonstrated the same mean difference in phase 3 as high-end users in phase 2, but with wider 95% agreement limits. Some recordings seemed to be twice the actual value. Health personnel, inexperienced in listening to hearts, may tap on both the first and second heart sounds, that is, tapping twice for each heart beat, a potential risk for errors in HR calculation even when auscultating without support from NeoTap. A qualitative study in our setting revealed that midwives did not assess HR by auscultation before the start of this study. Instead they palpated the cord or the chest.[34] The midwives, however, accurately assessed the metronome rhythm. Auscultation-focused training and awareness of the first and second heart sounds could potentially improve clinical HR assessment with the tapping method. Clinical studies have shown that training is crucial and repeated training of health personnel affects the management of patients.[35 36] It is likely that clinicians would have obtained better results due to prior experience in HR auscultation, and a training module for HR auscultation in resuscitation simulators could probably improve auscultation skills and performance of low-end users. Phase 3 shows few disagreements and narrow IQR ranges, and approximately three-fourths of HRs differed 20 or less from the true value in the 60–99 bpm and ≥100 bpm categories, pointing at a high probability of adhering to guidelines.

There is need for a low-cost, rapid and accurate alternative method for monitoring HR during neonatal resuscitation in low-resource to middle-resource settings. Rapid and accurate decision-making is crucial in neonatal resuscitation and PO is too slow to fulfil international resuscitation guidelines.[7 9 37] ECG is fast and accurate but may be difficult to apply on the wet torso of the neonate, leading to delayed application.[38 39] NeoTap or other apps for HR assessment are potentially faster than PO and ECG, offering an alternative way to fulfil international guidelines.[24 25] However, the reported acquisition times in phase 3 were possibly due to a misunderstanding of the 'tap at least three times for HR' feature of the app. Users should be reminded to tap until they feel confident of tapping the same pace as the HR they hear, still a swift method potentially leading to higher accuracy.

There are limitations to this study. Low-end users were skilled in neonatal resuscitation and were trained in Helping Babies Breathe shortly before the study started. The participants were part of an ongoing trial providing a better environment for auscultation. Less experienced healthcare providers in rural areas may produce inferior results. The gold standard is different for each of the three phases due to practical reasons, for example lack of ECG at the study site during phase 2. PO has high sensitivity and specificity but may display a too low HR during the first minutes of life.[40] PO in this study was used in neonates not in need of PPV at 120 s or more after birth, supporting the reliability of the PO data, and since NeoTap showed slightly higher HRs it points at NeoTap being accurate. The participants in phase 2 and 3 were not masked to the true value, introducing a potential bias, but the algorithm of NeoTap displays the average rate of the last three taps. This, combined with the very short acquisition times in both phases, de-emphasises this point. We had different users in the respective phases for practical reasons, making it harder to generalise the results. Most of the HR assessments in phase 3 were unsupervised, meaning timing of placement of ECG and first HR assessment was up to the user. Also, in phase 3, we could not identify the users since only the hands were caught on the videos; therefore, the number of users in this phase is an approximation. Lastly, we had few measurements of HR <100 bpm and especially <60 bpm, limiting the possibility of evaluating the importance of the results in clinical practice.

CONCLUSION

NeoTap provides a low-cost technology well adapted to the context of low-resource settings. It can be used in an inexpensive smartphone for swift and accurate HR registration. Clinical assessment by low-end users was less accurate and the authors suggest they may benefit from auscultation-focused training. Further studies are needed to demonstrate whether smartphone apps are useful in clinical practice.

Twitter Susanna Myrnerts Höök @SavingNeonates

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Contributors SMH was responsible for the study design, preparation of the study site, acquisition of data, data analysis and interpretation of data. She conducted the literature search and was responsible for the writing process of the manuscript and approval of the final draft. NJP contributed to study design and acquisition of data. He revised the work draft and approved the final draft. FC, an independent statistician, contributed to the analyses of the data. He revised the work draft and approved the final draft. CL, JB and JN contributed to study design, manuscript revision and approved the final draft. TT contributed to interpretation of data, manuscript revision and approved the final draft. TA contributed to the study design, data analysis, manuscript revision and approval of the final draft.

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Patient consent for publication Not required.

Ethics approval The Institutional Review Board of Mulago National Referral Hospital, the Uganda National Council for Science and Technology, the National Drug Authority of Uganda, and the Regional Committee for Research Ethics in Norway (REK South-East 2013/2096 and 2017/989) approved the protocols.

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Annex I

PARTICIPANTS INDENTIFICATION CARD

Neonatal Supraglottic Airway Trial

Study identification number

Study enrolment date (dd/mm/yyyy)

Date of birth (dd/mm/yyyy)

Name of caretaker (initials)

Address of caretaker

Day 7 return date (dd/mm/yyyy)

Study office number

Staff ID Date (dd/mm/yyyy)

CRF version 4.0 27st September 2018

CASE REPORT FORM 1

Neonatal Supraglottic Airway Trial

Study identification number ☐☐☐☐☐☐☐☐ Initials of mother ☐☐☐

Birth information

1. Date of birth ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy) 4.Ventilation time ☐☐ ☐☐ (min:sec)

2. Time of birth ☐☐ ☐☐ (hr:min) 5.Time when resuscitation terminated ☐☐ ☐☐ (hr:min)

3. Time from birth to table ☐☐ ☐☐ (min:sec)

Resuscitation

6.Type of resuscitation

☐ FMV ☐ i-gel ☐ Others, specify ☐☐☐☐☐☐☐☐

Cross over

7.Cross over to the other device?

☐ Yes ☐ No

If yes, fill all that apply

8.Time of cross over ☐☐ ☐☐ (min:sec) Comment ☐☐☐☐☐☐☐☐

☐ Cross over from i-gel to face mask

☐ Cross over from face mask to i-gel

☐ Cross over because of failed PPV

☐ Cross over because of mask/i-gel leak

☐ Cross over because of airway blockage

☐ Cross over because of absent/poor chest movement

☐ Cross over due to failed insertion

☐ Cross over due to absent/poor heart rate improvement

☐ Cross over because of other reasons, specify ☐☐☐☐☐☐☐☐

Advanced resuscitation

9.Did the patient receive advanced resuscitation from the supervising physician?

☐ Yes ☐ No

If yes, fill all that apply

☐ Patient was intubated with an endotracheal tube

☐ Patient received chest compressions

☐ Patient received intravenous drugs for resuscitation

☐ Others, specify ☐☐☐☐☐☐☐☐

Staff ID ☐☐☐☐ Date ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy)

CASE REPORT FORM 1
Neonatal Supraglottic Airway Trial

Study identification number

Patient status

10. Was the patient hospitalized?

☐ Yes ☐ No

11. Did the patient die after resuscitation?

☐ Yes ☐ No ☐ Suspected FSB

Patient information

12. Sex of the baby

☐ Male ☐ Female ☐ Don't know

13. Birth type

☐ Single ☐ Twin ☐ Others (specify)

14. Weight ☐ (grams)

Patient perinatal history

15. Mode of delivery

☐ Vaginal delivery ☐ Ceasarean section ☐ Assisted delivery

16. Delivered by

☐ Doctor ☐ Midwife ☐ Others, specify

17. APGAR

☐ 1 min ☐ 5 min ☐ 10 min

Adverse events

18. Blood from mouth

☐ Yes ☐ No

19. Vomiting

☐ Yes ☐ No

20. Laryngospasm

☐ Yes ☐ No

21. Other adverse events

☐ Yes ☐ No

(If yes specify)

Minor malformations

22. Minor malformations ☐ Present ☐ Absent

Staff ID Date (dd/mm/yyyy)

CASE REPORT FORM 2

Neonatal Supraglottic Airway Trial

Study identification number ☐ Initials of the mother ☐

Birth

1. mother's age ☐ (years) ☐ Don't know

2.Did mother attend antenatal clinic

☐ Yes ☐ No

3.Order of birth

☐ 1st born ☐ 2nd born ☐ Others, specify ☐

4. Pregnancy complications?

☐ Yes ☐ No If yes, specify ☐

Mother perinatal history

5. Date of admission (mother) ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy)

6. Birth problems

☐ Yes ☐ No If yes, specify ☐

7. Time of onset of labour ☐☐ ☐☐ (hr:min) ☐ Don't know

8. Time of rupture of membranes ☐☐ ☐☐ (hr:min) ☐ Don't know

9. Anaesthesia: General anaesthesia. ☐ Yes ☐ No

Spinal anaesthesia ☐ Yes ☐ No

If given before baby is born, specify

☐ IV Pethidine ☐ IV Ketamine ☐ IV Fentanyl ☐ IV Diazepam ☐ IV Midazolam

Others specify: _____

10. Clear amniotic fluid

☐ Yes ☐ No ☐ Don't Know

11. Meconium stained amniotic fluid

☐ Yes ☐ No ☐ Don't Know

12. Foul smelling amniotic fluid

☐ Yes ☐ No ☐ Don't Know

Staff ID ☐☐ ☐☐ Date ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy)

CASE REPORT FORM 3 (Follow-up)
Neonatal Supraglottic Airway Trial

Study identification number ☐☐☐☐☐☐☐☐☐☐ Initials of the mother ☐☐☐

1. Day of follow up

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Patient information

2. Is the baby alive?

☐ Yes ☐ No

3. If no, date of death ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy)

Thompsons score

4. TONE

☐ Normal (0) ☐ Hyper (1) ☐ Hypo (2) ☐ Flaccid (3)

5. LOC

☐ Normal (0) ☐ Hyperalert, stare (1) ☐ Lethargic (2) ☐ Comatose (3)

6. FITS

☐ Normal (0) ☐ <3 per day (1) ☐ >2 per day (2)

7. POSTURE

☐ Normal (0) ☐ Fisting, cycling (1) ☐ Strong Distal Flexion (2) ☐ Decerebrate (3)

8. MORO

☐ Normal (0) ☐ Partial (1) ☐ Absent (2)

9. GRASP

☐ Normal (0) ☐ Poor (1) ☐ Absent (2)

10. SUCK

☐ Normal (0) ☐ Poor (1) ☐ Absent± bites (2)

11. RESPIRATION

☐ Normal (0) ☐ Hyperventilation (1) ☐ Brief apnea (2) ☐ Apnea (3)

12. FONTANEL

☐ Normal (0) ☐ Full, not tense (1) ☐ Tense (2)

TOTAL SCORE ☐☐☐

Staff ID ☐☐☐ Date ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy)

CASE REPORT FORM 3
Neonatal Supraglottic Airway Trial

13. ADVERSE EVENTS

☐ Yes ☐ No

☐ Bleeding ☐ Stridor ☐ Airway obstruction ☐ Visible trauma

☐ Localized infection ☐ Sepsis Others (specify) ☐

14. ANTICONVULSANTS TREATMENT

☐ Phenobarbital ☐ Phenytoin Others (specify) ☐

15. HYPOGLYCEMIA

☐ Yes ☐ No If yes, specify lowest blood glucose level ☐ (g/dl)

16. CIRCULATION

☐ Pallor ☐ Anaemia ☐ Dehydration ☐ Delayed Capillary Refill

17. TEMPERATURE

☐ Hypothermia ☐ Fever Temperature ☐ degrees Celsius

18. COAGULATION

☐ Petechia ☐ General Coagulopathy Localized bleeding (specify) ☐

19. RESPIRATION

☐ Ventilated (severe apnea) ☐ CPAP ☐ O_2

20. OTHER SIGNS
Specify ☐

21. TREATMENT
Specify ☐

Staff ID. ☐☐ Date ☐☐☐ (dd/mm/yyyy)

CASE REPORT FORM 4 (day 7 follow up)
Neonatal Supraglottic Airway Trial

Study identification number | | Initials of the mother | |

Patient information

1.Is the baby alive?

☐ Yes ☐ No

2. If no, date of death | | | | (dd/mm/yyyy)

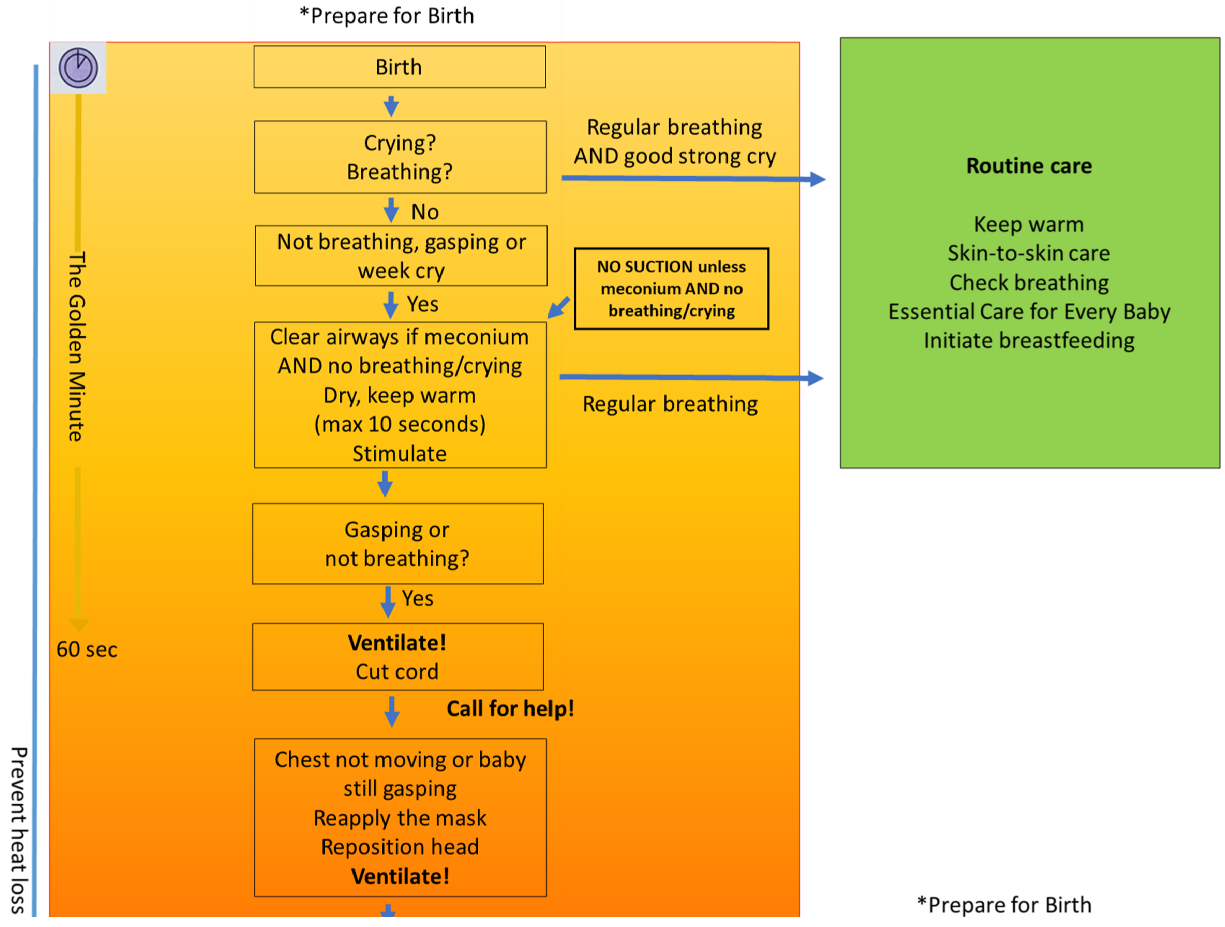
3. Has the baby been hospitalized?

☐ Yes ☐ No

Staff ID | | | Date | | | | (dd/mm/yyyy)

Annex II

Neonatal Resuscitation Mulago Hospital



Effective ventilation for 30 seconds with **room air**

Helper check heart rate with stethoscope or cord

Heart rate >60

Heart rate <60

Call for help for chest compression

Continue ventilation until baby breathing or seek advice from doctor
Re-evaluate every minute
Consider intubation

Continue ventilation!
Helper initiates chest compressions
3 chest compression to 1 breath
Seek advice from doctor

Consider
Volume expansion: I.V. N/S or R/L
10 ml/kg and
if in need of Intubation consult doctor

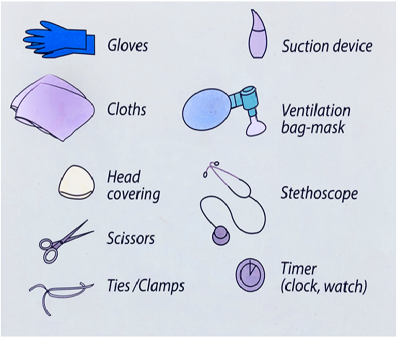
Regular breathing

If regular breathing and normal heart rate (>100)
Prevent heat loss (normal temperature 36.5-37.5)
Oxygen if cyanosed
To SCU

Piece of advice:

- If no heart rate after 10 min resuscitation, including at least 5 min CPR 3:1, seek advise from doctor before considering to terminate resuscitation
- If no spontaneous breathing after 20 min resuscitation seek advise from doctor before considering to terminate resuscitation even if heart rate is normal

*Prepare for Birth



Disinfect equipment after use

Ref.
Uganda Clinical Guidelines 2016
ILCOR Guidelines 2015
Helping Babies Breath V2 Action Plan

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