# Small newborns in post-conflict Northern Uganda:

## Burden and interventions for improved outcomes

Beatrice Odongkara

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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MAKERERE UNIVERSITY

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# Dedication

To God the Almighty Father, and my beloved parents Engineer Peter Odongkara and Nancy Akello. Father, you always say *"Gwok ma dako bene mako lee (a female dog also catches animals)".* Thank you for instilling in me the resilience of the African girl child this way. Mother, you never lifted your knees off the ground, always softly saying, *"... atina, abedo aber ... (my child, it will be fine).*

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## The scientific environment

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# Abbreviations

| | |
|---|---|
| AAP | American Academy of Pediatrics |
| AGA | Appropriate for Gestational Age |
| BMI | Body Mass Index |
| BMV | Bag Mask Ventilation |
| BPD | Bronchopulmonary dysplasia |
| CME | Continuing medical education |
| DALYs | Disability Adjusted Life Years |
| DHS | Demographic and Health Survey |
| ENAP | Every Newborn Action Plan |
| FGR | Foetal growth restriction |
| GAPPS | Global Alliance to Prevent Prematurity and Stillbirth |
| GBD | Global Burden of Disease |
| GEE | (multivariable) Generalised Estimation Equation |
| HBB | Helping Babies Breathe |
| HC II-V | Health Centre II–V |
| HCWs | Health Care Workers |
| HF | Health Facility |
| HIC | High-Income Countries |
| IDPs | Internally Displaced Persons |
| ILCOR | International Liaison Committed on Resuscitation |
| IPT | Intermittent Preventive Treatment for malaria |
| IQR | Interquartile range |
| IRB | Institutional Review Board |
| IUGR | Intrauterine growth restriction |
| LBW | Low Birthweight |
| LIC | Low-Income Country |
| LMICs | Low- and Middle-Income Countries |
| LMP | Last Menstrual Period |
| LRA | Lord's Resistance Army |
| MDGs | Millennium Development Goals |
| MIC | Middle-Income Country |
| MNCH | Maternal Newborn Child Health |
| MNH | Maternal Newborn Health |
| MO | Medical Officer |
| MoH | Ministry of Health |
| MRTS | Maturity rating total scores (using New Ballard Scores) |
| NCDs | Non-Communicable Diseases |
| NEC | Necrotizing enterocolitis |
| NMR | Neonatal Mortality Rate |
| NRP | Neonatal Resuscitation Program |
| ODK | Open Data Kit |
| PB | Preterm birth |
| RBG | Random Blood Glucose |
| RDS | Respiratory distress syndrome |

| | |
|---|---|
| SB | Stillbirth |
| SBAs | Skilled Birth Attendants |
| SD | Standard deviation |
| SDGs | Sustainable Development Goals |
| SGA | Small for Gestational Age |
| SP | Sulfadoxine and Pyrimethamine |
| SSA | Sub-Saharan Africa |
| SSC | Skin-to-skin care |
| TBA | Traditional Birth Attendant |
| TFR | Total Fertility Rate |
| UBoS | Uganda Bureau of Statistics |
| UDHS | Uganda Demographic and Health Survey |
| UN | United Nations |
| UNCST | Uganda National Council of Science and Technology |
| UNICEF | United Nations Children Fund |
| US | Ultrasound |
| UTI | Urinary Tract Infections |
| YLDs | Years Lived with Disability |
| YLLs | Years of Life Lost |
| VHTs | Village Health Teams |
| WHA | World Health Assembly |
| WHO | World Health Organization |
| WoG | Weeks of Gestation |

# Abstract

*Introduction:* A small newborn can be the result of either a low birthweight (LBW), or a preterm birth (PB), or both. LBW can be due to either a preterm appropriate-for gestational-age (preterm-AGA), or a term small-for-gestational age (term-SGA) or intrauterine growth restriction (IUGR). An IUGR is a limited in-utero foetal growth rates or foetal weight < $10^{th}$ percentile. Small newborns have an increased risk of dying, particularly in low-resource settings. We set out to assess the burden, the modifiable risk factors and health outcomes of small newborns in the post-conflict Northern Ugandan district of Lira. In addition, we studied the use of video-debriefing when training health staff in Helping Babies Breathe.

*Subjects and methods:* In 2018-19, we conducted a community-based cohort study on 1556 mother-infant dyads, nested within a cluster randomized trial. In our cohort study, we estimated the incidence and risk factors for LBW and PB and the association of LBW with severe outcomes. We explored the prevalence of and factors associated with neonatal hypoglycaemia, as well as any association between neonatal death and hypoglycaemia. In addition, we conducted a cluster randomized trial to compare Helping Babies Breathe (HBB) training in combination with video debriefing to the traditional HBB training alone on the attainment and retention of health worker neonatal resuscitation competency.

*Results:* The incidence of LBW and PB in our cohort was lower than the global estimates, 7.3% and 5.0%, respectively. Intermittent preventive treatment for malaria was associated with a reduced risk of LBW. HIV infection was associated with an increased risk of both LBW and PB, while maternal formal education (schooling) of ≥7 years was associated with a reduced risk of LBW and PB.

The proportions of neonatal deaths were many-folds higher among LBW infants compared to their non-LBW counterparts. The proportion of neonatal deaths among LBW was 103/1000 live births compared to 5/1000 among the non-LBW.

The prevalence of neonatal hypoglycaemia in our cohort was 2.5%. LBW and PB each independently were associated with an increased risk of neonatal hypoglycaemia. Neonatal hypoglycaemia was associated with an increased risk of hospitalisation and severe outcomes.

We demonstrated that neonatal resuscitation training with video debriefing, improved competence attainment and retention among health workers, compared to traditional HBB training alone.

*Conclusion:* In northern Uganda, small infants still have a many-fold higher risk of dying compared to normal infants. In addition, small infants are also at more risk of neonatal hypoglycaemia compared to normal infants. Efforts are needed to secure essential newborn care, should we reach the target of Sustainable Development Goal number 3.2 of reducing infant mortality to less than 12/1000 live births by 2030.

# Original papers

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

Paper I:

**Beatrice Odongkara**, Victoria Nankabirwa, Grace Ndeezi, Vincentina Achora, Anna Agnes Arach, Agnes Napyo, Milton Musaba, David Mukunya, James K Tumwine, Thorkild Tylleskar. Incidence and risk factors for low birthweight and preterm birth in post-conflict northern Uganda: a community-based cohort study. *Amended manuscript*

Paper II:

**Beatrice Odongkara**, Victoria Nankabirwa, Vincentina Achora, Anna Agnes Arach, Agnes Napyo, Milton Musaba, David Mukunya, Grace Ndeezi, Thorkild Tylleskar, James K Tumwine. LBW was associated with an eight-fold increased risk of neonatal death in post-conflict Northern Uganda: a community-based cohort study. *Manuscript*

Paper III:

Mukunya D, **Odongkara B**, Piloya T, Nankabirwa V, Achora V, Batte C, Ditai J, Tylleskar T, Ndeezi G, Kiguli S, Tumwine JK. Prevalence and factors associated with neonatal hypoglycaemia in Northern Uganda: a community-based cross-sectional study. *Trop Med Health*. 2020 Nov 4;48(1):89. doi: 10.1186/s41182-020-00275-y.

Paper IV:

**Odongkara B**, Tylleskär T, Pejovic N, Achora V, Mukunya D, Ndeezi G, Tumwine JK, Nankabirwa V. Adding video debriefing to Helping-Babies-Breathe training enhanced retention of neonatal resuscitation knowledge and skills among health workers in Uganda: a cluster randomized trial. *Glob Health Action*. 2020 Dec 31;13(1):1743496. doi: 10.1080/16549716.2020.1743496.

Appendix:

Paper I in its published form: **Beatrice Odongkara**, Victoria Nankabirwa, Grace Ndeezi, Vincentina Achora, Anna Agnes Arach, Agnes Napyo, Milton Musaba, David Mukunya, James K Tumwine, Thorkild Tylleskar. Incidence and risk factors for low birthweight and preterm birth in post-conflict northern Uganda: a community-based cohort study. *Int J Environ Res Public Health. 2022;19:12072.*

# Introduction

This chapter defines concepts related to small newborns during the neonatal period. In addition, we review literature on the global, regional and national burden, known risk factors and low-cost interventions for improved outcomes of small newborns.

## 1.1 The neonatal period is a time of vulnerability

In the human life cycle, the early childhood (under-five or U5) period is the time of most risk, with the foetal and neonatal period, in turn, being its most vulnerable phase.[1,2] Small newborns are even more vulnerable than their normal birthweight counterparts.[2,3] Small newborns may be the result of a baby with either low birthweight (LBW) or a preterm birth (PB), or a combination of the two.[3] Every year, close to 44% of the world's under-five deaths occur in the neonatal period, with sub-Saharan Africa and South-east Asia contributing the largest share of this burden, compared to the rest of the world.[4] By 2016, LBW and PB were among the top five leading causes of neonatal mortality and post-neonatal morbidity worldwide, and these small newborns, therefore, need special attention.[3,5,6]

### 1.1.1 Low birthweight

Low birthweight is defined as weight <2.5 kg at birth.[7] It can be due to either a preterm birth that may be appropriate for gestational age (AGA), or a term birth that is too small for the corresponding gestational age (Figure 1) or foetal growth restriction (FGR or intrauterine growth restriction, IUGR).[8] Small for gestational age (SGA) is defined as a birthweight <10$^{th}$ percentile for gestational age.[8] SGA may be further categorized into term-small for gestational age (term-SGA), or preterm-small for gestational age (preterm-SGA). An intrauterine growth restriction (IUGR) is defined as limited in-utero foetal growth rates or foetal weight < 10$^{th}$ percentile.[8]

### 1.1.2 Preterm births

Preterm birth is defined by the World Health Organization (WHO) as any birth before 37 completed weeks of gestation, or fewer than 259 days since the first day of a woman's last menstrual period (LMP), or any birth between 23 and 37 completed weeks of gestation to a live infant weighing >500g to ≤2.5kg.[7] It is categorized by gestational age as extremely preterm (24 to <28 weeks), very preterm (28 to <32 weeks), and moderately preterm (32 to <37 weeks).[7] Figure 1 summarises the definitions of LBW and its constituent PB and SGA by gestational age.

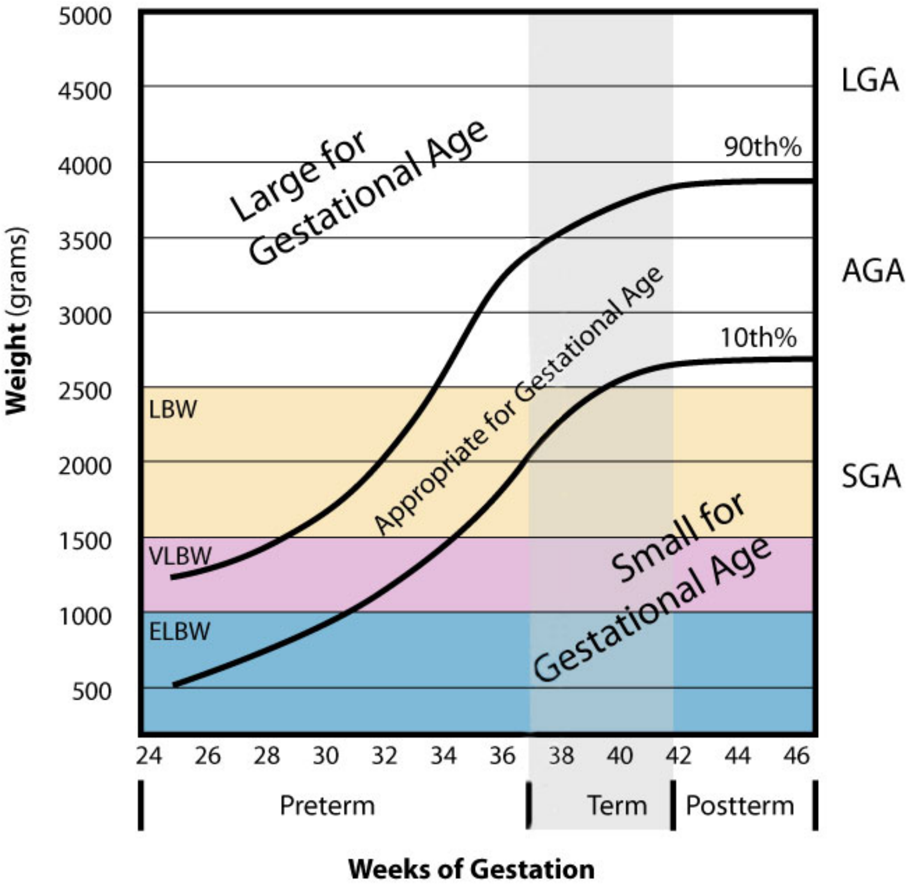



***Figure 1. Definitions by weeks of gestation and birthweight of different categories of small newborns.***
*LBW low birthweight, VLBW very low birthweight, ELBW extremely low birthweight. (Adapted from Yehudamalul, https://commons.wikimedia.org/w/index.php?curid=8980869)*

## 1.2 Causes of low birthweight and preterm birth

Fetal growth restriction, also known as intrauterine growth restriction (IUGR), is a common complication of pregnancy that has been associated with a variety of adverse perinatal outcomes.[8] There is a lack of consensus regarding terminology, aetiology, and diagnostic criteria for fetal growth restriction, with uncertainty surrounding the optimal management and timing of delivery for the growth-restricted foetus.[8] An additional challenge is the difficulty in differentiating between the foetus that is constitutionally small and fulfilling its growth potential and the small foetus that is not fulfilling its growth potential because of an underlying pathologic condition.[8] IUGR is a common pathway to small birth size (LBW and PB) with a variety of maternal, placental and foetal causes summarized in Box 1.[8]

**Box 1. Aetiology of Fetal Growth Restriction**

- Maternal medical and environmental conditions
  - Pre-gestational diabetes mellitus
  - Renal insufficiency
  - Autoimmune disease (e.g., systemic lupus erythematosus)
  - Cyanotic cardiac disease
  - Pregnancy-related hypertensive diseases of pregnancy (e.g., chronic hypertension, gestational hypertension, or preeclampsia)
  - Antiphospholipid antibody syndrome
  - Substance use and abuse (e.g., tobacco, alcohol, cocaine, or narcotics)
  - Teratogen exposure (e.g., cyclophosphamide, valproic acid, or antithrombotic drugs)
  - Infectious diseases (e.g., malaria, cytomegalovirus, rubella, toxoplasmosis, or syphilis)
- Foetal factors
  - Genetic and structural disorders (e.g., trisomy 13, trisomy 18, congenital heart disease, or gastroschisis)
  - Multiple foetuses
- Placental disorders and umbilical cord abnormalities

*Adapted and modified from ACOG Practice guidelines on foetal growth restriction 2021*[8]

The diagnosis of foetal growth restriction requires a specialised obstetrician and Doppler ultrasound for accurate serial uterine artery velocitometry and foetal biometrics measurements.[8] In a resource-limited community settings with little to no access to ultrasound diagnostic tools during pregnancy, identification of IUGR and SGA is challenging. Infants with either conditions are, however, at risk of the same complications of meconium aspiration, asphyxia, hypoglycaemia and hypothermia.[8] Due to the diagnostic challenges for IUGR and SGA in low resource settings rural northern Ugandan district of Lira, the scope of this thesis was limited to low birthweight and preterm birth.

From LMICs a number of additional maternal, foetal and placental factors have been associated to LBW and/or PB (small birth size).[9] Maternal factors that have been associated with low birthweight and preterm birth include maternal age, socio-economic, maternal ill-health, and excessive physical activities.[9] The age of the mother, either young (teenage 12-16 years) or old (≥35 years) has been linked to increased risk of small birth size.[9] Low maternal socio-economic and education status has been associated with small birth size.[9] Furthermore, maternal ill-health during pregnancy such as malaria and HIV infection, low body mass index (BMI) or low gestational weight gain, have also been associated with small birth size.[9] A history of having given birth previously to a small infant has been linked to LBW and/or PB recurrence in subsequent pregnancies.[9] Whereas some studies report increased risk of small birth size among women who do excessive physical work, a 2013 meta-analysis found little to no effect of the same on small birth sizes.[10]

### *Malaria and small newborns*

Malaria in pregnancy is a known risk for adverse pregnancy and birth outcomes, including small newborns and neonatal death. The sequestration of infected red blood cells in the placenta, leads to a cascade of host responses which may lead to placental inflammation, abnormal development, and compromised nutrient transport to the growing foetus (Figure 2).[11]

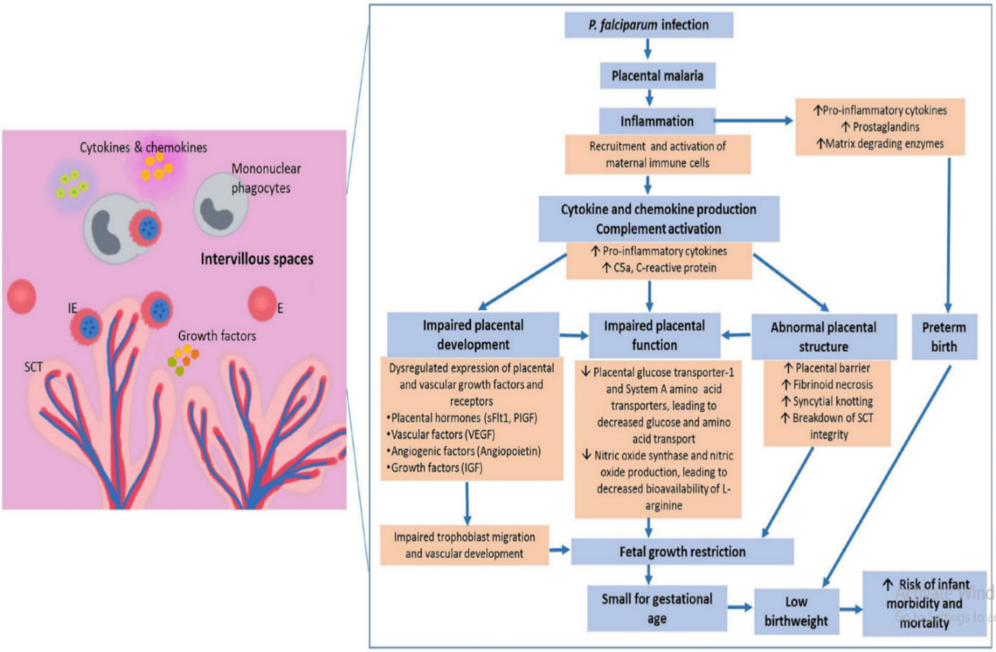



**Figure 2. Mechanisms of LBW and PB in malaria in pregnancy**
*Adopted from Chua CLL et al 2021.*

### *Placental diseases and intrauterine growth restrictions*

Several mechanisms by which maternal hypertension, pre-eclampsia, and other placental diseases causing IUGR have been described, in Table 1.

Table 1: Placental diseases and mechanisms of intrauterine growth restriction.

| Disorders | Mechanisms | Diagnosis |
|---|---|---|
| Pre-eclampsia, hypertension[12] | Not fully understood, but placental ischaemia triggers a cascade of events leading to the release of antiangiogenic factors into the maternal circulation, with resultant maternal endothelial dysfunction, multi-organ failure and placental insufficiency | Severe hypertension, end organ dysfunctions (coagulopathy, proteinuria) Clinical, Doppler ultrasound scan, histopathology, biomarkkers[13,14] |
| Placenta praevia (placental implantation near or over the cervical os)[15] | Insufficient placental perfusion from less uterine blood flow to the lower segment than the fundus Antepartum haemorrhage – foetal hypoperfusion | Late gestational ultrasound scan to detect persistence and or resolution |
| Abruption (placental separation after 20 weeks of gestation and before delivery)[16] | Unclear, however, utero-placental perfusion insufficiency, infarction and infections | |

## 1.3 The global burden of LBW and PB

### 1.3.1 Global, regional and national estimates of LBW

Of the 140 million infants born worldwide in 2014, an estimated 20 million (14%) were born with low birthweight (<2.5 kg).[17] Ninety percent (18/20 million) of LBW infants were born in low- and middle-income countries (LMICs).[17] In sub-Saharan Africa, LBW prevalence varied from 7.0% to 18.0%, with the highest prevalence observed in malaria-infested areas in Tanzania.[18] According to the Uganda Bureau of Statistics (UBoS) 2011, 10.4% of all live-born infants nationwide and 11.4% in the northern part of the country were LBW.[19] The global estimates for LBW and its subtypes are summarized in Table 2.

Table 2. The estimated global LBW rates and subtype constituents.

| Low birth weight globally | Global estimates | Percent |
|---|---|---|
| LBW overall[20] | 20 million | (100%) |
| LBW-Term-SGA | 11.8 million | (59%) |
| LBW-Preterm-S/AGA [21] | 8.2 million | (41%) |

*LBW low birthweight, N (%) number (percentage), S/AGA small/appropriate for gestational age*

### 1.3.2 Global, regional, and national estimates of PB

In 2010, an estimated 15 (11.1%) million preterm infants were born worldwide.[22] The global PB estimates ranges from 5% in Europe to 18% in some sub-Saharan African countries.[22] Sub-Saharan Africa and South Asia contribute 52–60% of the global PB burden.[22] In Uganda, reports of the proportion of PBs range from 4.1% to 15%,[22,23] In communities of post-conflict northern Uganda, however, its true burden is unknown.

## 1.4 Gaps in LBW and PB estimates

The global estimates of the burden of small newborns (LBW and PB) for low-income countries including Uganda, are unreliable, as they depend on very low-quality health facility data and non-existent vital data registries.[24] Estimates based on statistical modelling using limited five-yearly demographic and health surveys (DHS) and facility-based studies, are assumption-dependent and may not be representative of the population.[22,24,25] In addition, most reports rely on maternal recall of birthweight and birth size during the five years preceding DHS interviews.[19] This is so even when <58% of infants are weighed at birth, and >40% are home births without access to weighing scales.[20] We therefore argue that, it is insufficient to rely on five-yearly DHS by most high burden countries to estimate the burden of small newborns. This health data gap makes it difficult to interpret the global, regional, and national burden of small newborns and to plan interventions and track progress; hence the need for more research in our setting.

Furthermore, WHO recommends countries to report all live births and foetal losses from 22 weeks of gestation, but the legal requirements and actual practice at the country level differ from the recommendations.[24] In Uganda, the minimum gestational age for perceived foetal viability is 28 weeks (personal experience and observation in-hospital/health facility).[24,25] Any infant born before this is deemed an abortus because they rarely survive postnatally in absence of neonatal intensive care. This is also true for other low-resource settings, where infants born before 28 weeks of gestation are less likely to survive beyond the hospital settings.[26] All these decrease the reliability of the reported estimates of LBW and PB.

Care, survival, and numeration of the world's most vulnerable citizens (the small newborns) is vital for the national development of a nation. It provides a sensitive test for health systems' responsiveness as well as an accountability for world leaders.[27] The WHO Every Newborn Action Plan (ENAP) emphasised counting all birth outcomes, including low birthweight, preterm births, neonatal death and stillbirths.[27] We also need to focus more attention on the leading causes of neonatal death around the time of birth, targeting small newborns in particular. This is because a healthy start in life is the cornerstone for human capital development and economic progress.[28] To achieve the post-2015 MDG era of grand convergence of health and human potential within a generation, there is need to improve birth outcomes (reduced LBW and PB).[29] This is because birth size (being a small newborn) determines short-term progress in reducing stillbirths, neonatal and child deaths.[29] It also determines long-term progress, including decreasing non-communicable diseases (NCDs) in adulthood.[29] Bridging this data gap may help nations to have an up-to-date context-based information on the status of small newborns for planning and interventions to improve outcomes. Thus, there is a need to count the proportion of, and factors associated with small newborns and subsequent effects of small newborns on neonatal adverse outcomes such as death, hospitalisation and hypoglycaemia in post-conflict northern Uganda.

## 1.5 Estimating gestational age for preterm birth identification

Several methods have been studied and used to estimate gestational age (GA).[24] During pregnancy, the ultrasound scan between 12-18 weeks of gestation is the gold standard and the preferred method. In high income countries, the best obstetrics method using an algorithm-based approach to pregnancy dating by ultrasound and last menstrual period is used.[24] In resource- limited settings where access to ultrasound during pregnancy is limited, several methods are used to estimate the gestational age of the infant after birth. These methods include the, last menstrual period and newborn examination using for instance the Dubowitz' and the New Ballard scoring (NBS) systems. Some of these methods is discussed in the next section.

### 1.5.1 The ultrasound method

The ultrasound (US) scan before 16 weeks of gestation (WoG) is the gold standard for gestational age estimation.[30] Later in pregnancy (14-34 WoG), the INTERGROWTH21 Research group reported good validity and reliability in gestational age determination of using head circumference alone, or in combination with foetal length.[31] They also recommend that for third trimester ultrasound scan, a follow-up ultrasound in two or three weeks for fetal growth velocity to confirm accurate GA, is required.[31] Foetal biometrics in later trimesters may predict gestational age up to 98% with some imprecision of up to 5.1 – 16.5 days and 7.1 – 23 days, around the mean GA at 14 – 34 and 34 – 36 weeks, respectively.[31] Ultrasound is still not universally used as it requires expensive equipment and expertise – which is often lacking in resource-limited settings and non-existent in post-conflict lower health facilities in the rural Northern Uganda (field observation).

### 1.5.2 Dubowitz' method

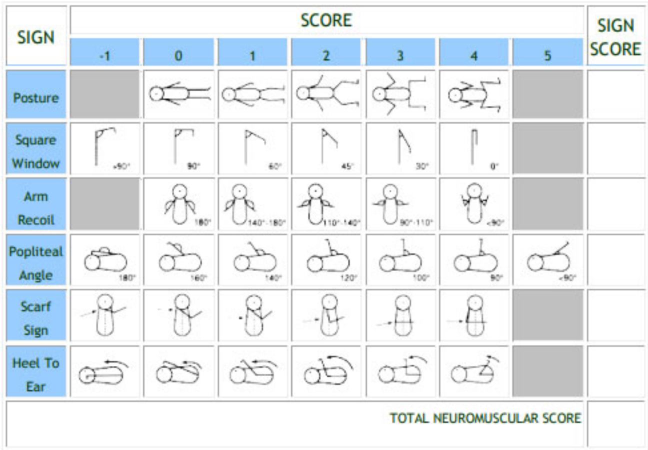
Postnatal gestational age estimation is done when no ultrasound is available. The Dubowitz' scoring method for gestational age estimation assesses the infant and uses 10 neurological criteria and 11 external/skin criteria.[32] The total score of both is then converted to GA in weeks.[32] This method has been found to overestimate GA by 2.57

weeks compared to the ultrasound method (gold standard).[33] Each of the components (neurologic, external/skin criteria and total scores) had a high correlation of between 0.90 – 0.97, with gestational age by last menstrual period (LMP) among mothers with reliable dates.[32,34] This method is problematic in settings where very few women know or remember their LMP dates, and the long list of features used in scoring makes it difficult for administration in community settings.

### 1.5.3 The New Ballard Scoring systems

The New Ballard Scoring system (NBS) reliably assesses foetal maturity up to 94% at birth, and 92% by 7 days of life.[35] The respective inter-rater agreement (reliability) at 12 and 96 hours for infants born from 26 weeks of gestation are 0.97 and 0.92 (excellent).[35] It is also reported to have a good individual NBS components correlation with individual GA dates, by ultrasound ranging between 0.72 – 0.87.[35] The intra-rater agreement (validity) of the NBS at 12 and 96 hours were 97% and 92%, respectively. Compared to the gold standard, the respective intra-cluster correlation for intra-rater agreement (validity) on days 1, 5, and 7 were 0.94, 0.94 and 0.92.[36] It is, therefore, suitable for GA determination in infants, whose mothers do not have access to gestational age assessment by ultrasound, or with unreliable last menstrual period (LMP) dating.[33,37,38]

The NBS consists of five neuromuscular and six physical maturity criteria, with each component score ranging from -1 to 5, except for physical maturity features for posture and arm recoil (Figure 3). Each section has a total score of 25. The sum of neuromuscular and physical maturity scores (maturity rating total scores or MRTS) range from -10 to 50, corresponding to GA by maturity, rating 20-44 weeks.



**The New Ballard Score** www.ballardscore.com

**NEUROMUSCULAR MATURITY**

| SIGN | SCORE -1 | 0 | 1 | 2 | 3 | 4 | 5 | SIGN SCORE |
|---|---|---|---|---|---|---|---|---|
| Posture | | | | | | | | |
| Square Window | >90° | 90° | 60° | 45° | 30° | 0° | | |
| Arm Recoil | | 180° | 140°-180° | 110°-140° | 90°-110° | <90° | | |
| Popliteal Angle | 180° | 160° | 140° | 120° | 100° | 90° | <90° | |
| Scarf Sign | | | | | | | | |
| Heel To Ear | | | | | | | | |
| | | | | | | | TOTAL NEUROMUSCULAR SCORE | |

**MATURITY RATING**

| TOTAL SCORE | WEEKS |
|---|---|
| -10 | 20 |
| -5 | 22 |
| 0 | 24 |
| 5 | 26 |
| 10 | 28 |
| 15 | 30 |
| 20 | 32 |
| 25 | 34 |
| 30 | 36 |
| 35 | 38 |
| 40 | 40 |
| 45 | 42 |
| 50 | 44 |

| SIGN | SCORE -1 | 0 | 1 | 2 | 3 | 4 | 5 | SIGN SCORE |
|---|---|---|---|---|---|---|---|---|
| Skin | Sticky, friable, transparent | gelatinous, red, translucent | smooth pink, visible veins | superficial peeling &/or rash, few veins | cracking, pale areas, rare veins | parchment, deep cracking, no vessels | leathery, cracked, wrinkled | |
| Lanugo | none | sparse | abundant | thinning | bald areas | mostly bald | | |
| Plantar Surface | heel-toe 40-50mm: -1 <40mm: -2 | >50 mm no crease | faint red marks | anterior transverse crease only | creases ant. 2/3 | creases over entire sole | | |
| Breast | imperceptable | barely perceptable | flat areola no bud | stippled areola 1-2 mm bud | raised areola 3-4 mm bud | full areola 5-10 mm bud | | |
| Eye / Ear | lids fused loosely: -1 tightly: -2 | lids open pinna flat stays folded | sl. curved pinna; soft; slow recoil | well-curved pinna; soft but ready recoil | formed & firm instant recoil | thick cartilage ear stiff | | |
| Genitals (Male) | scrotum flat, smooth | scrotum empty, faint rugae | testes in upper canal, rare rugae | testes descending, few rugae | testes down, good rugae | testes pendulous, deep rugae | | |
| Genitals (Female) | clitoris prominent & labia flat | prominent clitoris & small labia minora | prominent clitoris & enlarging minora | majora & minora equally prominent | majora large, minora small | majora cover clitoris & minora | | |
| | | | | | | | TOTAL PHYSICAL MATURITY SCORE | |

Gestation by Dates ______ weeks

Birth date ______ Hour ______ am pm

APGAR ______ 1 min ______ 5min ______

Scoring

| | |
|---|---|
| Gest. Age by Maturity Rating | ________weeks |
| Time of Exam | Date__________ Hour______ am pm |
| Age at Exam | ________hours |

Signature of Examiner

______________________________ M.D. / R.N.

**References :**

Ballard JL, Khoury JC, Wedig K, *et al*: New Ballard Score, expanded to include extremely premature infants. *J Pediatrics* 1991; 119:417-423.

http://ballardscore.com/Pages/ScoreSheet.aspx

***Figure 3. The New Ballard Score Sheet.***

## 1.6 Outcomes of small newborns (LBW and PB)

Small newborns (LBW and PB) are at increased risk for short- and long-term health problems.[39] In the short-term, they may be at risk of neonatal death, hospitalisation, hypoglycaemia, birth asphyxia and respiratory distress syndrome (RDS), feeding difficulties, and infections.[39] Small newborns are also at risk of postnatal growth failure or stunting.[40] They may develop long-term complications such as neurodevelopmental, visual and hearing impairments, non-communicable diseases (NCDs) including asthma, diabetes mellitus and hypertension.[39] Most of these reports from high-income countries are for very low birthweight and/or extremely preterm infants; while there is little data on moderately LBW and PB infants in resource-limited settings including post-conflict northern Uganda. Small newborns may therefore be at increased risk of both short-term neonatal and long-term post neonatal growth and health related challenges.

### 1.6.1 When, where and why do newborns die?

#### *When do newborns die?*

According to the World Health Organization, a neonatal death is death of a live-born infant before or on 28 completed days of life.[7] Neonatal mortality is the number of neonatal deaths per 1000 live births. About 75% of the neonatal deaths happen in the first week of life, with the main causes of death in LMICs including Uganda, being small size (low birthweight or preterm birth) and/or having birth asphyxia.[41] There were, however, no studies reporting on this in post-conflict northern Uganda prior to our study inception.

#### *Newborns in four worlds (where do newborns die?)*

The WHO Every Newborn Action Plan (ENAP) advocacy group reiterates that every newborn, born in any setting and condition, have equal rights to access equitable health care because, all human lives are equal and matter.[27] Whereas all newborns have equal rights at birth, they are born into four different worlds, that is, in high-income countries (HICs), in middle-income countries (MICs), in low-income countries (LICs) in health facilities, and in LICs at home (the unknown world).[42] The setting a newborn is born into, determines his/her chances of immediate and long-term survival. There is an enormous inequality in child survival between and within the four worlds.[43] For instance, compared to an infant born in a HIC, an infant born in an LIC is 13-times more likely to die in the first five years of life and even worse, an infant born in sub-Saharan Africa (SSA) is 20-folds more likely to die in the first five years of life.[43] Furthermore, an infant born in an African LMIC setting is >10-times more likely to die in the neonatal period than those in HIC.[44,45] Preterm birth, neonatal infections and birth asphyxia cause ≥90% of neonatal deaths in low resource settings including Uganda.[46] Yet >75% of preterm infants can survive, with essential newborn care practices, even in the absence of neonatal intensive care.[39] Essential newborn care practice includes immediate skin-to-skin contact to maintain warmth, infection control, and early initiation of breastfeeding or expressed breast milk for cup feeding.[47] We therefore need, low-resource, context-based studies to better position our newborns in any of these worlds for better planning and intervention.

These survival gaps have continued to increase over the last decade, with faster reductions in neonatal mortality rates in HICs, and no or small reductions observed in LMICs.[43] The disparities also occur within countries, for instance, children from rural and poor families that lack basic household education have higher neonatal mortality rates, than those born in families with more resources.[48] Even in countries where the neonatal and under-five mortality have declined, inequalities between rich and poor still exist.[48]

### *Small newborns are at increased risk of dying*

By the year 2016, both LBW and PB were the leading direct causes of neonatal and under-five deaths, and illness in the world, including Uganda.[5,49-51] The risk of dying for infants in the neonatal period is very unequally spread – the risk is increased for LBW and PB compared to normal weight and term infants and for infants born in an LMIC compared to those born in an HIC.[52] Being born small (PB or LBW) in low-resource settings increases the risks of neonatal death seven- and two-folds, respectively, compared to being born with the same condition in HICs.[52] Small newborns in LMIC thus carry a double risk of dying.

### 1.6.2 Causes of neonatal mortality among LBW and PB infants

Small newborns risk both short- and long-term complications. The short-term complications may include hypothermia, infections, breathing problems such as severe respiratory distress syndrome (RDS), feeding problems such as hypoglycaemia, feeding difficulties or even necrotizing enterocolitis (NEC).[53]

Respiratory distress syndrome is the single most common complication claiming the lives of preterm infants.[54] The RDS may further be complicated by respiratory disturbances (cough, wheezing, and infections) with potential increased economic burden on families and health systems.[54] Failure to establish respiration may be associated with failure to recruit functional lung capacity that leads to the development of bronchopulmonary dysplasia (BPD), and consequently, increased need for mechanical ventilation.[55]

Other factors that may increase neonatal death among small newborns may include maternal ill-health, health system challenges and armed conflicts.[56,57] Numerous studies have reported an association between maternal ill-health including infections, diabetes mellitus, hypertension and malaria in pregnancy and neonatal death.[57,58] Finally, there are health systems factors associated with increased risk of neonatal death including small newborns having inadequate access to health care, understaffing, inadequately trained human resources for health and lack of drugs and equipment.[9] We shall discuss some common causes of neonatal death (hypoglycaemia, and birth asphyxia). In addition, the effect of armed conflicts on neonatal health and the historical background of Lira district are discussed in the next sections.

#### *Neonatal hypoglycaemia*

Intrauterine life is characterised by a continuous supply of nutrients, including glucose, through the maternal fetal placental barriers.[59] Term neonates have transitional hypoglycaemia in the first 1-3 days of life, after which they usually attain blood glucose values similar to those of older infants, children and adults.[59,60] A quantitative definition of hypoglycaemia in newborns has long remained elusive, with no consensus on a unified definition. The Paediatric Endocrine Society (PES), however, defines neonatal hypoglycaemia as plasma glucose <50mg/dl (<2.8mmol/l, based on evidence of cognitive impairment (neuroglycopenia) observed with plasma glucose <50mg/dl.[60]

There are several factors associated with neonatal hypoglycaemia, such as being small-for-gestational-age (LBW and/or PB), delayed initiation of breastfeeding, hypothermia, birth asphyxia, maternal diabetes mellitus, neonatal sepsis and, in rare cases, hyperinsulinism, and congenital abnormalities.[61-63] The consequences of neonatal hypoglycaemia may include neonatal seizures, brain injury, neurocognitive dysfunction, suboptimal growth, or even neonatal death.[64-68]

### *Birth asphyxia*

Birth asphyxia, also known as neonatal encephalopathy, is when a foetus or newborn fails to adapt to extrauterine life, resulting from interrupted placental blood flow and subsequent suffocation[69] or from failure to initiate breathing after birth. Both fetal (LBW, PB, or small newborns) and maternal (poverty, pre-/eclampsia, antepartum haemorrhage, anaemia) factors may cause birth asphyxia.[57,58,70] As with mortality, the incidence of birth asphyxia is higher (>99%) in LICs, compared to HICs.[71] It is responsible for almost one million neonatal deaths annually.[71] It also accounts for up to 50% of deaths in the first week of life. Most term infants are initiating breathing after birth, however, about 10% of all newborns may need some assistance to begin breathing, while 1% may require extensive resuscitation.[72] Most of the 10% may be successfully resuscitated using methods such as stimulating the infant by using basic neonatal resuscitation (drying, clearing the airways, and giving ventilation).[71] Use of a bag and mask, could save four out of every five babies who need resuscitation.[73] Advanced resuscitation with endotracheal intubation and oxygen is only required for a minority of asphyxiated babies.[74] In addition, survivors of birth asphyxia may have both acute (hypoglycaemia, hypothermia, seizures) and chronic (cerebral palsy, blindness, delayed neurodevelopment, and poor school performance) morbidity.[75-77]

### 1.6.3 Armed conflicts and newborn health

Armed conflict is an important public health problem.[56,78,79] More than half of the countries in SSA, including Uganda, have experienced armed conflicts, in the period since the end of the cold war.[80,81] In 2005, the United Nations listed Uganda among nine SSA countries with armed conflicts and high total fertility rates (TFR), above 6 children per woman.[82] War also has devastating effects after (post-) conflict across all (social, political and economic) sectors of society.[83-85] In addition, armed conflicts may lead to the destruction of health care and other important infrastructure including health worker deaths and health worker migration, famine, destroyed road access, high fertility rates with resulting poor maternal and newborn health.[86,87] Conflict-affected countries including post-conflict Northern Uganda, also experience increased mortality among refugees and internally displaced persons (IDPs), including infants and neonates.[88,89]

The high TFR with armed conflicts may be due to low maternal and/or female education status, increased school dropouts, and the need to replace the children from high infant mortality.[90,91] The high TFR seen in poor countries compared to rich countries during war, may also be a coping strategy to insecurity, especially when a large family is a dominant form of economic and social security (personal observation and experience).

In 2009, UNICEF reported a negative reversal on gains in maternal health following conflicts.[92] Only a few studies have examined the long term effects of a protracted armed conflict on the burden and outcomes of small newborn infants, 10 years after the guns have gone silent in Northern Uganda.[93] With the wealth of information on armed conflicts, we thus hypothesize that there may be a high burden of small newborns with associated increased risk of neonatal adverse outcomes (death, and/or hospitalisation and hypoglycaemia) in post-conflict Northern Uganda.

### 1.6.4 Recent history of Northern Uganda, Lira district

Between 1986 and 2006, there was little information on maternal and newborn health from Northern Uganda, in the national (Uganda) health and demographic surveys

(UDHS).[94-96] Even the strategic plans for the health sector for the same regions had hardly any indicators on newborn, specifically small newborn (LBW and PB) infants.[97] At the time of the study design and inception period in 2016/17, the only report available on newborn health status from the region was the one where UNICEF and the Ministry of Health conducted a survey on maternal and newborn health (MNH).[98] They reported that there was poor reporting to non-existent record-keeping of the same in health facilities across the country, including Lira and Arua, that represented Northern Uganda.[98]

The Lord's Resistance Army (LRA) insurgency moved into Lira district in 2002 resulting into massive population displacement in the district and surrounding areas (personal and lived experience). As the security situation improved, the district experienced a massive return of IDPs in 2006/07. An estimated 350,000 persons left IDP camps to return to their home villages within a period of 14 months. These villages had few to no functional health facilities for maternity, because either the war destroyed them, or the health workers fled from the conflict, and were unwilling to return to their workstations (personal observation and experience during fieldwork).

In the 2010 Uganda Demographic and Health Survey (UDHS), about 11.5% of infants were born LBW or reportedly smaller than average baby. The neonatal mortality rate was 33/1000 live births, compared to the nation's 27 / 1000 live births, and the PB rates and maternal mortality ratio were unknown.[99] In 2012, the district had a low proportion of health facility deliveries (<60%), a high neonatal mortality and above all, non-existent data on most of the child health indicators, including small newborns. Furthermore, the prevalence, associated factors and outcomes of neonatal hypoglycaemia among small newborns compared to normal newborns was unknown for northern Uganda.

The social disruption, lack of schooling and displacement caused by the 20 years of conflict in the region may have modified the burden and some of the known risk factors for neonatal and birth outcomes including small birth size. Few studies exist to describe the burden of LBW and PB during the post-conflict period in northern Uganda.[3]

### 1.6.5 Interventions to reduce LBW and PB burden and mortality

To ensure favourable outcomes of pregnancy, birth and the neonatal period, the Every Newborn Action Plan (ENAP) was launched in 2014.[100] ENAP aimed to provide impartial high quality implementation of care packages for every woman and newborn, in collaboration with national and international partners worldwide.[100] Many scholars argue that around 66% of the neonatal deaths are preventable with cheap and proven interventions, such as skilled birth attendance (SBA).[47,100]

#### *Interventions along the continuum of care*

Several interventions such as family planning, girl child education and women empowerment, micronutrient supplementation (folic acid and iron), and proper nutrition during pregnancy, have been shown to reduce LBW and PB.[101] In addition, antenatal screening and treatment of maternal infections and illnesses; blood pressure and blood glucose control; control of vector borne diseases, using intermittent preventive treatment (IPT) for malaria; deworming, and active malaria case management, have also been shown to be effective. These interventions can be provided as an integrated care package, along the continuum of care, from preconception, to the post-partum period.[101]

#### *Interventions during labour and childbirth*

Interventions during the time of labour and birth include skilled birth attendance, clean birth, early initiation of breastfeeding, skin-to-skin care (SCC), and the availability of prompt neonatal resuscitation with bag and mask ventilation are required, to increase the likelihood of survival for small new-borns.[47,101] Prompt establishment of respiration at birth is a vital action for the survival of small newborns. Despite the availability of evidence-based cost-effective interventions for improved neonatal survival during the antenatal and postnatal period, skilled birth attendance during labour and child birth (time of the most need for baby and mother) is still limited in low-resource settings including sub-Saharan Africa.[102]

### Interventions to improve maternal and newborn health outcomes

Interventions to improve outcomes for maternal newborn health (MNH) at community, district and health facility levels exist.[103] At a community level, interventions that improve MNH outcomes include; generation of funds for transportation, postnatal home visits, women peer support groups and training of traditional birth attendants and mid-level health worker care.[103,104] Conversely, many interventions such as outreach clinics, continuing medical education (CME), problem-based learning, clinical guidelines implementation and critical appraisal, have showed inconclusive or mixed results on the quality of MNH care or outcomes.[105]

Social support during pregnancy, in-service training and specialised midwifery care, have reportedly improved MNH outcomes at the facility level.[105] In addition, burnout and stress management training, multi-disciplinary meetings and feedback sessions for health care workers (HCWs) performance, and motivation improve these outcomes.[105] Despite this evidence of effective interventions for MNH outcomes from HICs, the generalizability of these findings to all populations in LMICs, including post-conflict settings is difficult.

Although very few MNH outcomes were observed at the district level, user directed financial incentives such as conditional cash transfers and maternal voucher systems, have been reported to improve quality of care and MNH outcomes in some instances.[106,107] At this level, there is limited evidence concerning the effectiveness of leadership, supervision, health information systems, and staffing models on MNH outcomes.

### The Helping Babies Breathe neonatal resuscitation training program

In response to high neonatal mortality, the American Academy of Pediatrics (AAP) developed a low cost neonatal resuscitation programme named 'Helping Babies Breathe' (HBB), for training birth attendants in LMICs.[102] This programme has now been taken over by WHO and the Healthy Newborn Network partners.[108] The Helping Babies Breathe programme is a simulation-based training, using a manikin

('NeoNatalie') to impart neonatal resuscitation knowledge and skills, to skilled birth attendants in low-resource settings.[102,109] Between 2012 – 2016, close to 400,000 birth attendants were trained in HBB across the globe. Despite this massive HBB training scale-up, the reduction in neonatal mortality at 28 days has remained slow in most low-resource settings, especially in sub-Saharan Africa, including Uganda.[109] There is evidence of improved knowledge and skills performance (competence) immediately post training, and reduction in early (24 hours), but not in late (28 days) neonatal deaths in these settings. [110]

A decline in knowledge and skills performance over time could be due to lack of refresher training. The optimal timing for refresher training is not known.[109] The relative rarity of birth asphyxia and lack of resuscitation practice among trained or skilled birth attendants, may also explain this knowledge and skills decay.[111-113] Although knowledge and skills are important in resuscitation, evidence from a cohort study in Tanzania, also noted that having the same eight months post-training, did not translate into actual practice.[114,115]

For the HBB training programme to positively impact neonatal mortality from asphyxia, we need to put several efforts in place. These may include continuing medical education using refresher training, support supervision, and mentorship.[116] It also includes addressing other health systems factors such as availability of adequate and functional resuscitation equipment and supplies.[116] Furthermore, the need for motivated human resources for health workers on duty 24/7 to provide skilled births, prompt newborn resuscitation and post resuscitation debriefing, cannot be overemphasized.[116]

To succeed with institutional births, there is a need to increase trained staff at all levels of training, and to maintain most-needed skills through refresher training at several yet to be clarified intervals.[102,117] To this effect, several training programmes have been developed such as neonatal resuscitation program (NRP) and HBB, which have shown good results in reducing neonatal death.[102] In our study setting, health care workers (birth attendants) have been trained in HBB by the Ministry of Health and its partners (personal field experience and observations in years of service). There are no clear guidelines as to how many resuscitation procedures are needed per year, to maintain skills and how often optimal refresher training should be done (personal field experience and observations in years of service). None the less, it is necessary to maintain effective and efficient resuscitation competence.[117]

### *Newborn resuscitation knowledge and skills for improved neonatal outcomes*

In low-resource settings, the basic resuscitation equipment for health facilities includes a firm and flat resuscitation surface/table, a suction device, a heat source, and ventilation device (bag and mask).[117] Effective ventilation devices for low-resource settings should be reasonably priced, and easy to use. For successful handling of birth asphyxia in these settings, affordable, effective and efficient ventilation using a bag-and-mask is one of the most important tasks.[117] Bag and mask ventilation is the standard of care, and affordable versions are available for low-income countries.[117] For appropriate fitting, it is important to have masks sizes for both term and preterm births.[117]

Neonatal resuscitation with room air is safe and effective.[138] Several studies comparing room air and oxygen for neonatal resuscitation, found the former being safer and superior for newborn resuscitation, with lower mortality and complications such as oxidative stress.[118-120] Therefore, WHO recommends room air for resuscitation of most children at the community level, and at facilities without routine availability of oxygen.[117]

Prompt management of birth asphyxia with neonatal resuscitation is important if we are to achieve the SDG 3.2 of reducing neonatal and under-five mortality to <12, and 25 per 1000 live births by 2030, respectively. Enhancing SBAs' skills to reduce neonatal mortality through prompt resuscitation also reduces disability adjusted life years (DALYs), years lived with disabilities (YLDs), and years of life lost (YLL).[121] Consequently, it reduces the economic burden of disease from encephalopathy and cerebral palsy.[121] Besides, Hans Rosling argues that when child (neonatal) mortality is reduced, a woman is under less pressure to replace the lost child, resulting in a reduction in birth and fertility rates.[122]

Home deliveries without skilled birth attendance (SBA) are still common in low-income countries.[123] Even for those who deliver within health facilities, there may not be guaranteed access to quality care.[124] Some studies in low-resource settings, for instance, report ≤50% of staff in health facilities to have resuscitation skills, few retain their skills even if they have been trained, due to lack of practice.[124-126] This loss of knowledge and decrease in skill retention over time may impact caregiver performance. However, refresher training improves performance and reduces inter-professional group differences.[125,127] Therefore, further studies are required to determine the optimal timing and frequency for refresher training, and time for decay of skills in neonatal resuscitation skills.

In addition, frequent staff rotations, health workforce migration/attrition and shortages of health workforce (paediatricians and obstetricians), all jeopardise the quality of newborn care in our study settings (personal observations and experience in service). A study in South Africa showed that avoidable factors for asphyxia-related deaths in rural hospitals, were mostly health-worker related.[128] Inadequate monitoring and poor partograph use were the most common causes. Shortages of medical doctors, obstetricians, paediatricians and midwives are also contributing factors to the absence of quality obstetric and newborn care in many parts of the LICs, including Uganda.[129] The need for resuscitation cannot be predicted in most newborns, because most of those that require resuscitation have no known risk factors. Therefore, there is need for SBAs to have appropriate knowledge and sufficient skills, to provide prompt high quality neonatal resuscitation whenever needed.[130]

### *Debriefing*

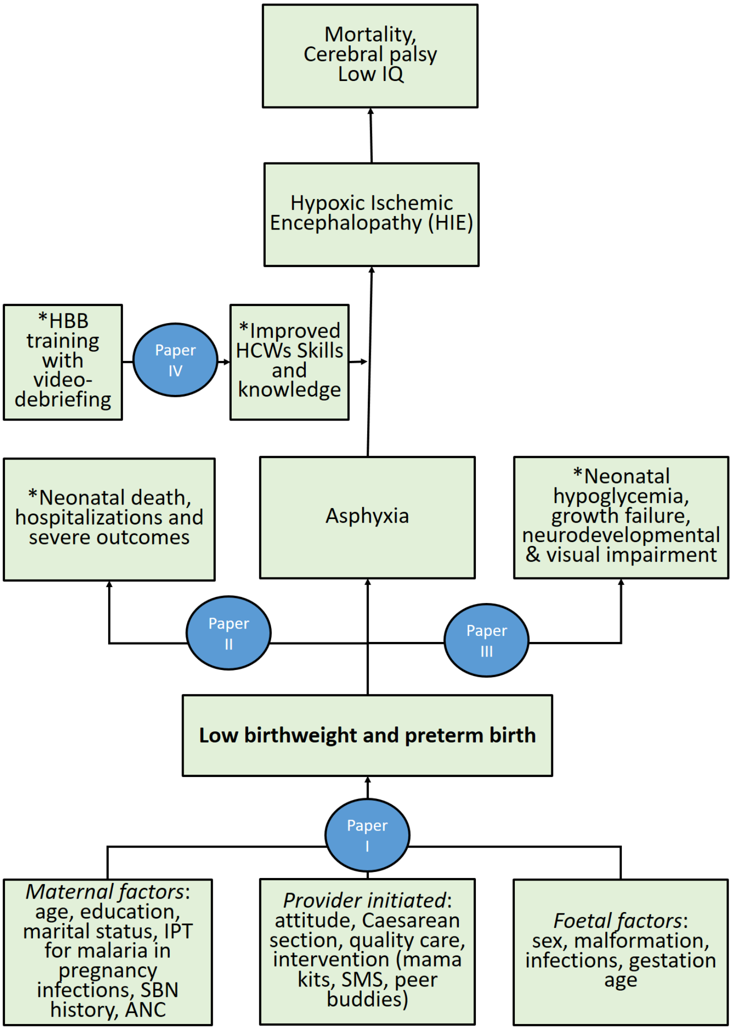
Debriefing is a process of obtaining feedback after a given task or activity through questioning with the aim of improving subsequent behaviour, cognition, perception, or performance.[131] It is a learner-centred feedback strategy, aimed at reinforcing learning, and improving the care and safety of patients.[131] Debriefing has its roots in the military and has been used since World War II, when Samuel Lynn Atwood Marshall subjected soldiers to review battles soon after, to document the events.[132] They each described up to the tiniest details about what unfolded, from the beginning to the end of the battle, what happened, how they felt, what their behaviours meant, and how it affected the other combatants. They used this information to plan future battles for better performance.[132] Since then, other disciplines in health, education, aviation, engineering and psychology have used debriefing to enhance learning and perfect skills, following simulations.[132]

In health care, debriefing has been employed as part of a growing trend towards simulation-based learning. The aim is to ensure patient safety. It has, however, been noted that simulated learning experience and debriefing differs from real life experiences, when faced with the real patients (neonates) in clinical settings, in terms of emotional experiences.[133,134] Debriefing, therefore, bridges the gap between experiencing the event, and learning from the same event or activity, and planning subsequent actions.[133]

There are two methods of debriefing in simulation training: video-assisted debriefing and verbal debriefing. Video-assisted debriefing uses pre-recorded sessions to guide the debriefing process. There are two debriefing tools used to guide and evaluate healthcare debriefing, the PEARLS (Promoting Excellence and Reflective Learning in Simulation) approach to health care debriefing, and the debriefing experience checklists.[134-136] These tools ensure feedback and key learning points are generated and focused learning is provided from the identified learning gaps.

# 2. Conceptual approach

The root causes and consequences (outcomes) of small newborns, are summarised in Figure 4.




HCWS health care workers, HBB helping babies breathe, SNB small newborns, ANC antenatal care, SMS short text messages, IPT intermittent preventive treatment, * the factors and outcomes which were studied and presented in this thesis.

***Figure 4. Conceptual framework for the small newborns in post-conflict Northern Uganda.*** *The papers in the thesis are marked with blue circles.*

Some cost-effective interventions to prevent preterm deliveries such as antenatal screening, treatment of maternal illnesses (infections) and micronutrient supplementation, have been implemented along the continuum of care, to prevent small newborns. Before and during pregnancy, maternal antenatal attendance, micronutrient supplementation, screening and treatment of maternal illnesses (hypertension, diabetes, malaria and urinary tract infections may prevent small newborn deaths. In the event that preterm labour sets in, during labour and delivery, maternal corticosteroid for foetal lung maturation is administered to the mother. In addition, essential newborn care such as neonatal resuscitation, thermal care (skin-to-skin contact) and early initiation of breastfeeding are done to prevent asphyxia, hypothermia and hypoglycaemia. Postnatally, continued thermal care, exclusive breastfeeding, early identification and treatment of neonatal infections and prevention of infection by hand washing and cord care practices, reduce the risks of neonatal death and/or hospitalisation (severe outcomes) among small newborns.

We investigated the burden of LBW and PB and their short-term consequences (neonatal hypoglycaemia, neonatal death and/or hospitalisation). In addition, we studied the burden and consequences of neonatal hypoglycaemia among small newborns. Finally, we assessed the effect of a (low-cost) modified neonatal resuscitation training, using video debriefing on frontline SBAs' skills and knowledge (competence), to provide respiratory support at birth to manage birth asphyxia among newborns, including our infant cohort in Northern Uganda.

## 2.1 Problem statement

The worldwide and local scarcity of reliable population-based, generalizable data on small newborn (LBW and PB) and neonatal hypoglycaemia burden and outcomes, is worrying. This lack of high-quality real-time data makes planning and tracking interventions and progress towards SGD 3.2 2030 goal in low-resource post-conflict settings, including the Lira district, difficult.

Although there is evidence showing improved maternal newborn health outcomes through cost-effective interventions such as in-service training, specialized midwifery and support supervision in HICs, there is limited data on the effects of the same interventions in low-resource, post-conflict settings. Without regular practice, knowledge and skills in neonatal resuscitation and newborn care decline overtime, post-training. This decrease in skill retention may be explained by the relative scarcity of opportunities to practice neonatal resuscitation skills and frequent staff rotations within and outside maternity units. Little is known about the effect of adding video debriefing to current HBB training curriculum on knowledge and skills retention among these frontline in-service skilled birth attendants in post-conflict northern Uganda.

The International Liaison Committed on Resuscitation (ILCOR) recommends regular refresher training for re-certification after every 2 years for basic neonatal resuscitation. In Uganda, there are no national guidelines on the frequency of refresher training. Several agencies keep training the same health workers, without any scientific guidelines on the training frequency for skills retention (personal observation and field experience). These trainings are usually followed by support supervision and mentorship by master trainers from the Uganda Ministry of Health and its partners. During these support supervisory and mentorship visits there is no structured way of providing ongoing learning and feedback.[1] Furthermore, low staffing level of <50% and high staff turnover has worsened the situation. The trained staff are lost through internal (within hospital departmental rotation) and external (out of hospital/country) brain drain, and hence, are unable to provide the needed skills to ensure newborn survival, whenever needed. It is therefore unknown if adding video-debriefing to the standard neonatal resuscitation training using HBB will improve the skill and knowledge attainment and retention among SBAs in this study setting. Post-event video assisted debriefing used in high-risk industries such as aviation, and engineering has shown improvement in safety and reduction in mortality, however,

[1] Personal experience and participation in USAID ASSIST support supervision

this is not yet being practiced in our country, including the study setting. We hope that its inclusion will improve the care and survival of small newborns.

## 2.2 Rationale of the study

To achieve the SDG 3.2 target of neonatal mortality below 12 per 1000 live births by 2030, there is urgent need to generate post-conflict context specific data on the small newborns (LBW and PB) health burden and associated modifiable risk factors. In addition, there is a need to generate more knowledge on short-term adverse neonatal outcomes such as neonatal death, hospitalisation and hypoglycaemia. This new knowledge may inform policy formulation for planning and tracking progress towards SDG 3 agenda 2030 achievement. Furthermore, reducing the burden and modifiable risk factors for small newborns and neonatal death, with cost-effective interventions such as HBB training, may contribute to the achievement of Sustainable Development Goals 3.2.

Training, combined with video debriefing, may improve knowledge, skills, and care practices for small newborn among frontline health care workers and SBAs in post-conflict northern Uganda. This in turn, may reduce short-term complications of small newborns including neonatal death and/or hospitalisation and hypoglycaemia from birth asphyxia. Moreover, it may also reduce small newborn related long-term complications such as neuro-developmental, growth, hearing and visual impairments. This may further reduce the economic burden on families and health care systems, with consequent positive effect on human national capital development. Lastly, an innovative training method in newborn resuscitation using video debriefing may inform policies, programmes and practices in post-conflict settings. This may also provide more evidence on the best possible combination of training intervention strategies for improved SBA competence in newborn care. The training innovation may also improve performance through provision of feedback to health care providers and patient safety through appropriate skills application.

## 2.3 Hypotheses

We therefore hypothesize that

i. The incidence of LBW and PB in northern Uganda higher than the global estimates.
ii. Advanced maternal age >=35 years is associated with an increased risk of LBW and PB than maternal age 20-34 years.
iii. The proportion of neonatal death and or hospitalisation is higher among LBW infants compared to the non-LBW.
iv. LBW is associated with an increased risk of neonatal death and or hospitalisation compared to non-LBW.
v. The proportion of neonatal hypoglycaemia is the higher among newborn infants in the community of Northern Uganda compared to the global estimates.
vi. LBW is associated with an increased risk neonatal hypoglycaemia compared to non-LBW.
vii. Neonatal hypoglycaemia is associated with adverse neonatal outcomes compared to normoglycaemia.
viii. Adding video-debriefing to the standard helping babies breathe training compared to standard training only had no difference on health care workers' competence attainment.
ix. Adding video-debriefing to the standard helping babies breathe training compared to standard training only no difference in competence retention at 1-, 3-, and 6-months post training.

# 3. Aims and objectives

## 3.1 Aims

The overall aim of the study was to: assess the burden of, risk factors for and neonatal outcomes (neonatal death, hospitalisation, severe outcomes and hypoglycaemia) of small newborns in post-conflict northern Uganda, in order to suggest policy changes.

## 3.2 Specific objectives

1. To estimate the incidence and risk factors for preterm births and low birthweight in Lira district, Northern Uganda, Paper I.

2. To evaluate the association between low birthweight and neonatal death and/or hospitalisation, Paper II.

3. To determine the prevalence, risk factors and outcomes of neonatal hypoglycaemia among LBW and PB infants, Paper III.

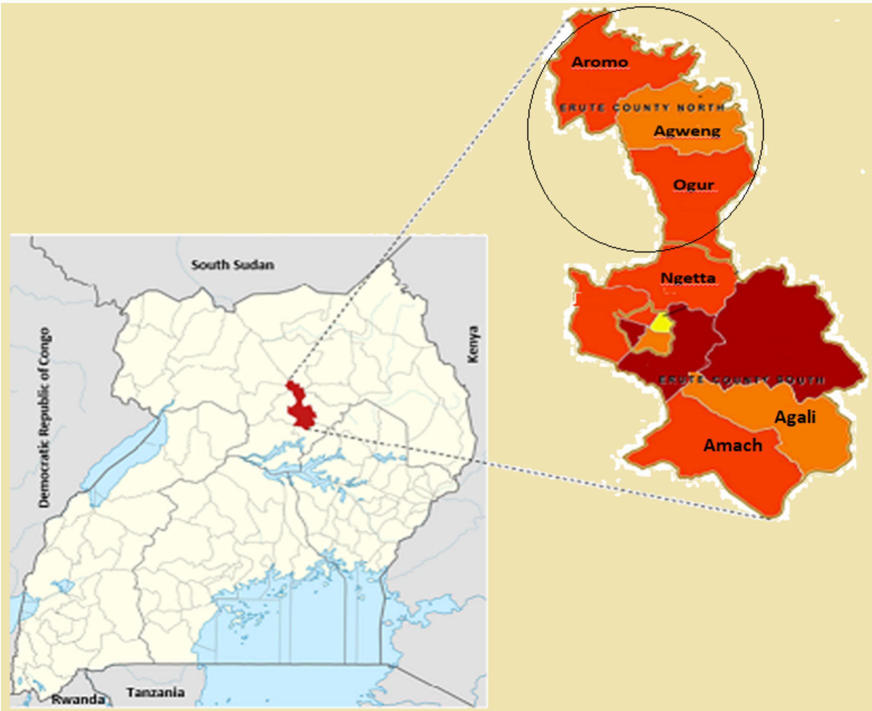
4. To assess the effect of helping babies breathe neonatal resuscitation training using video debriefing on SBAs' knowledge and skills attainment and retention at 1, 3 and 6 months, Paper IV.

# 4. Methodology

This chapter describes the context of the thesis in relation to armed conflicts. Furthermore, the study setting, participants, materials and methods are discussed.

## 4.1 Study site

We conducted the study in Lira District, Northern Uganda in a preparatory phase July-December 2017 and the actual data collection phase from January 2018, to March 2019 (Figure 5). Lira District had a population of about 400,000 people in 2010, living in 13 sub-counties, a city, and 751 villages.[19]




*The selected sub-counties are encircled*

***Figure 5. Map of Uganda showing Lira district and the three northernmost study sub-counties (ring).***

The main administrative and commercial centre in the district is Lira city, located 110 kilometres (68 miles) southeast of Gulu, the largest city in Northern Uganda. Most of the population is ethnic Langi, and the predominant language spoken is Lango.

The district was chosen based on its being a post-conflict area with poor maternal and child health indicators, low proportion of health facility deliveries, high neonatal mortality, and limited data on small newborns (LBW and PB), and neonatal hypoglycaemia, as risks for neonatal death, hospitalisation and severe outcomes (death and/or hospitalisation).[137] The study sites were Aromo, Agweng, and Ogur sub-counties; also chosen because they had the poorest maternal and child health indicators. Each sub-county had one health centre with maternity (health centre level III or IV), and two additional lower-level health centres without maternity (HC II). Two of the HC IIIs (Agweng and Aromo), however, were not conducting deliveries before the project inception.

The HBB training included HCWs from both private and public health units, providing maternity and delivery services to the communities of the Lira district of Northern Uganda. The Lira district health facilities (HFs) also received patients from neighbouring districts of Padere, Agago, Gulu, Albetong, and Oyam. The HF levels ranged from health centre II (HC IIs), to a regional referral hospital (Level VI). The inclusion of private HFs in the study was due to the fact that, most people seek delivery and newborn care services from these facilities (personal interaction with health centre in-charges and HBB trainees as well as observation from facility maternity registry). In addition, the private facilities are located closer to the communities than most government facilities (personal observation during fieldwork).

## 4.2 Target population

The study population included pregnant mothers recruited from the community during pregnancy and followed to delivery with their newborn infants at birth for

Papers I and III. Papers II and III also had mother infant-dyads, followed from delivery to 28 days for adverse neonatal outcomes.

We trained in-service health workers (nurses, midwives, clinicians, medical officers (MOs), and specialists) from public and private HFs for Paper IV. We also included staffs from other departments, to cater for staff rotation that happen frequently within and outside the maternity units. This ensured that most of the staff had the needed skills and knowledge to provide neonatal resuscitation care for newborn infants whenever taken to maternity units within or outside the health facility.

## 4.3 Sample size

The maximum sample size needed for the estimation of the incidence and risk factors for small newborns was calculated to be 1194 mother-infant dyads. This was deemed adequate for Papers I-III. In the survival Pluss main trial in which this study was nested, however, a total of 1877 mothers were recruited at ≥28 weeks of gestation, followed up to birth and 28 days postnatally. Of these, 1556 (for LBW burden and outcomes) mother-infant dyads with birthweight and 1279 (for PB and neonatal hypoglycaemia burden and outcomes) who had a gestational age estimate, birthweight, and blood glucose were analysed and presented in this thesis. Therefore, the study population and the sample size for Papers I-III was defined by the sample size of main trial. Since we had a finite population from which to sample our infants and for ethical reasons, we wanted to reach as many of the newborns as possible within two and seven days for birthweight and NBS respectively. We restricted our sample size to 1556 for all infants with birthweight to estimate the incidence of LBW. The total sample size of 1279 both birthweight and gestational age by NBS was used to study the burden of PB and neonatal outcomes of both PB and LBW. In addition, the 1279 mother-infant also had random blood glucose measurements. This enabled us to have a uniform comparison of outcomes in between groups, in addition to estimating the proportion of PBs who were LBWs and vice versa. In Paper III, a total of 1416 infants had blood glucose measurements and were all analysed and published.

Attempting to get the birthweight of everyone, where many deliveries still occurred at home, was a tall order and reaching 85% of infants at community level is reasonably good. There is still the risk, however, the mother-infant dyads reached at community level were the ones doing well whereas those struggling are the ones we fail to reach. It is therefore possible that the proportion of low birthweight and preterm birth in those not examined might have been higher than in the examined sample. The maternal demographic characteristics were similar between those examined and those not examined which is conventionally used as an indication that it is unlikely that the difference between the two groups is large. Nonetheless, we cannot exclude the possibility that the non-examined infants were worse off.

### 4.3.1 Sample size for the HBB with video-debriefing training

*Sample size for number of clusters*

We assumed a fixed number of clusters, a minimal intra-cluster variability and variable cluster sizes, and estimated a sample size to detect a 30% difference in competence attainment and retention between intervention arms were 20 clusters (10 in each arm).[138] We however have 26 health facilities providing delivery and newborn care in Lira. For ethical reasons, we included all the 26 health facilities with a total of 96 SBAs, of whom 86, were trained and followed up for 6 months.

## 4.4 Methods overview of the four thesis papers

Below is the summary of the design, participants and analysis used in each of the four papers presented in this thesis, with details found in each paper (Table 2).

### 4.4.1 Definitions of study variables and measurements

We present the study variable definitions and measurement methods in this section. Details of measurement method are found in each paper of the thesis and an overview in Table 3.

### Outcome measures

Primary outcomes in Paper I were low birthweight (LBW) and preterm birth (PB) while the secondary outcome was a composite of the two. A LBW was weight <2.5kg at birth, while a PB was defined as any birth before 37 completed weeks of gestation.[7] Incidence (risk) is the number new LBW or PB cases divided by total live births over a specified period of time. The incidence (risk) was expressed as the proportion of LBW or PBs during the study period from January 2018 to February 2019 to the total number of live births expressed as percentage or per 100 live births.

Table 3. Overview of the methods used for the 4 papers in the thesis.

| *Paper* | *Study design & analysis* | *Sample size* | *Exposure(s)* | *Outcome(s)* |
|---|---|---|---|---|
| *I* | *- Cohort study nested in a community/cluster-randomised trial<br>- Multivariable regression analysis* | *1556 and 1279 pregnant mother were analysed respectively, for LBW and PB burden* | *Maternal socio-economic factors (age, education, father's occupation, wealth index, domestic water source); maternal clinical factors (parity, previous history of PB/LBW, malaria infection and IPT in pregnancy, HIV infection, ANC attendance, Intervention); infant factors (sex)* | *Incidence of low birthweight and preterm birth* |
| *II* | *- Cohort study nested in a cluster randomized trial<br>- Multivariable analysis* | *1556 mother-infant dyads followed from birth to 28 days of life* | *Exposures same as in Paper I, plus LBW* | *Proportion of neonatal death, hospitalisation, or both (severe adverse outcomes)* |
| *III* | *Cross-sectional study* | *1279 mother-infant dyads with BW, RBG, and GA* | *Exposures same as in Paper II* | *Prevalence of neonatal hypoglycaemia* |
| *IV* | *- Cluster randomized trial<br>-Multivariable analysis* | *26 health facility (HF) clusters with 86 skilled birth attendants (SBAs)* | *Intervention (HBB training with video debriefing), HF level, SBAs age, sex, years in-service, education level, number of deliveries, resuscitation practices, prior HBB training.* | *1) knowledge and skills attainment, and 2) knowledge and skills retention* |

*LBW low birthweight, PB preterm birth, IPT intermittent preventive treatment, ANC antenatal care, HBB helping babies breathe, BW birthweight, RBG random blood glucose, GA gestational age, HF health facility, SBA skilled birth attendants,*

'Small newborn' was defined as the composite of LBW and/or PB. The incidence of small newborns was expressed as the proportion in percent of LBW and/or PB to the total population at risk.
Gestational age (GA) was estimated using the New Ballard Score (NBS) system, which employs both physical and neuromuscular maturation. The total physical maturation (PM) and neuromuscular maturation (NM), also known as maturity rating total scores (MRTS), was correlated with gestational age, recorded in completed weeks. The MRTS, ranging from -10 to 50, were then extrapolated to fetal age in weeks (20 to 44). For each 2.5 MRTS points, the gestational age increases with 1 week.[2] Birthweight was measured using a digital seca weighing scale (seca, Hamburg, Germany) and recorded to the nearest 2 decimal points in kilograms.

Primary outcomes for Paper II were neonatal death, and hospitalization while the secondary outcome was the composite of the two – adverse neonatal outcomes. Neonatal death was any demise of a live born baby within or on the 28$^{th}$ day of life. Verbal autopsies were done for all death reports. Hospitalisation was defined as hospital admission unrelated to labour and delivery for 24 or more hours. The presence of hospital admission was recorded when 'yes' was given as an answer to the question, "has your baby been admitted in the hospital since delivery?" and if the duration of admission was at least 24 hours.

Neonatal severe (adverse) outcome was defined as a composite of death and/or hospitalisation. Death and/or, hospitalisation rates were expressed per 1,000 live births. The choice of severe outcomes as secondary outcomes in this study is because hospitalisation and deaths have for long been used as proxies for neonatal morbidity.

The prevalence of neonatal hypoglycaemia was defined as the proportion of newborns with blood glucose <47mg/dl (<2.7mmol/l) in Paper III. Random blood glucose was measured in mmol/l using an On Call® Plus glucometer (ACON Laboratories, Inc., 10125 Mesa Road, San Diego, CA, USA), a point-of-care test. Under aseptic conditions, we obtained blood samples from the heels of neonates. The

[2] 1 week of gestation = (MRTS) / (estimated gestation age in weeks) = (50 - -10) / (44-20) = 60/24 = 2.5 MRTS

heel was first cleaned with alcohol swabs and dried with cotton. A single-use safety lancet was used to prick the heel. Maternal random blood glucose was also obtained at the same time from a finger prick. The team was closely supervised by a paediatrician who also doubles as paediatric endocrinologist and a medical doctor who had trained them on sample collection, observed their initial procedures, and occasionally sitting in during the recruitment visits to ensure the standard operating procedures were followed.

The two primary outcome measures in Paper IV were: 1) knowledge and skills attainment in the immediate (2 days) post-training period, and 2) knowledge and skills retention over a six-month follow-up period. Knowledge and skills attainment were defined as the percentage scores in knowledge and skills tests in the immediate (2 days) post-training period. Skills assessments were done using validated HBB programme tools (Bag-mask ventilation (BMV), Objective structured clinical examination, OSCE-A and OSCE-B checklists) for assessing neonatal resuscitation skills among SBAs using NeoNatalie manikin. Knowledge was assessed using the validated HBB multiple choice questions (MCQs).[139] Both knowledge and skills tests were obtained from the 2nd edition of the standard American Association of Pediatrics (AAP) HBB curriculum. Assessments were done pre- and post-intervention, and during subsequent longitudinal follow-up at one, three, and six months. The skills scores were obtained by taking the means scores for BMV, OSCE-A and OSCE-B. Scores were presented in percentages and analysed as continuous variables.

### *Exposure variables*

In Paper I – III we used the following exposure variables: maternal age was recorded in completed years and re-categorised into three groups as 12–19, 20–34, and 35–49 years; education was recorded in years of completed schooling and dichotomized as 0–6 and 7 or more years in school; marital status was categorised as binary variable into ‘married’ or ‘single/separated/divorced/widowed’; wealth index quintiles were calculated using a wealth index based on key household assets and classified ranging from the 1 ‘poorest’ to 5 ‘wealthiest’ quintiles. This was further sub-grouped into wealth three groups as follows: the lower 40% (1st – 2nd quintiles), the middle 40%

(3rd – 4th quintiles) and the upper 20% (5th quintile). Paternal occupation was categorized during analysis as farmer, employed or unemployed. Domestic water source was categorised as 'tap/borehole' or 'spring/well/river/ponds. History of prior small newborns was recorded as 'yes' if the mother had history of having had a small baby by her own assessment in prior pregnancy. Parity was the number of pregnancies the mother had before, and further re-categorised as 'prime gravida (first time mother)', '1–6' and '7 or more' children. The presence of maternal illnesses during pregnancy such as malaria or HIV were recorded as ('yes' 'no', or 'unknown') based on antenatal test results. Antenatal care (ANC) attendance was recorded as 'yes' if the woman attended antenatal clinic at least once during the current pregnancy. Facility delivery was recorded as 'yes', if the mother delivered from a health facility (maternity home, clinic, health centre or hospital). Maternal malaria intermittent preventive treatment (IPT) in pregnancy was recorded as 'yes', if the mother received sulfadoxine and pyrimethamine (SP) during pregnancy. Intervention was recorded as 'yes', if the mother received the Survival Pluss intervention package (advice on birthplace by a peer buddy, SMS messages, and a clean birth kit 'mama kit') during pregnancy. Infant's sex was recoded as "male" or "female". Post-natal infant bath was recorded as 'yes' if the infant was bathed since birth. Breastfeeding initiation was recorded as 'yes' if the mother initiated breastfeeding since birth.

In Paper IV, the occupation of the health workers was categorised as nurses/midwives, and clinical officers/doctors. Qualification was defined as the highest attained level of education: certificate, diploma, bachelor's degree, master's degree, and categorised as certificate and diploma or degree. HBB training experience was recorded as 'yes' if the person had ever attended at least one training. The time since the last training was recorded in months. Routine delivery and resuscitation practices were recoded as 'yes' if one provided delivery and neonatal resuscitation care at one's facilities on a regular basis or daily. The number of resuscitations per facility was counted from the birth registers. The number of newborn infants resuscitated was recorded from 0 to 10 or more and subsequently categorized was recorded as none versus one or more. The number of deliveries was physically counted as the total number of mothers delivered per facility. Health workers were also asked to record the average monthly number of deliveries attended and these were categorized as none, 1 to 9 and 10 or more. Health centre (HC) or unit type was categorised by level as HCII-III and HCIV or more. Number of years in-service were recorded in completed years and re-categorised as <5 or ≥5 years. Prior HBB training was recorded as 'yes' if one had at least a training before intervention.

### 4.4.2 Inclusion and exclusion criteria

In *Papers I – II*, a sub–sample of 1556 mother-infant dyads with birthweight and 1279 mother–infant dyads with GA by NBS, birthweight and blood glucose, of the 1877 recruited into the Survival Pluss cohort were included in this thesis. In *Paper III*, however, we analysed and published all the 1416 infants who had blood glucose measurements done. The Survival Pluss study included: mother-infant dyads from the participating communities at 28 or more weeks of gestation (*minimum gestational age for postnatal foetal viability in resource-limited settings);* mothers who had no intention of moving away from the study area within a year of enrolment; mothers who had no psychiatric illness that hindered the informed consent process. We excluded infants who: died at birth or before the NBS assessment; not reached within seven days for NBS; had congenital abnormalities (anencephaly, spina bifida and exomphalos); and those whose parents declined newborn examinations.

In *Paper IV,* we included both public and private health facilities (HFs) with health care workers and skilled birth attendants (SBAs) providing delivery and newborn care services, and excluded one community vaccinators and two laboratory technicians, who turned up for training and were neither providing delivery nor newborn care.

## 4.5 Study procedures

In Papers I – III, prior to recruitment, research assistants were trained on the study protocol, weight measurement, use of the electronic data collection tool, and the open data kit (ODK) software (https://opendatakit.org/). Pregnant mothers were identified by community recruiters, who informed the study team. The research assistants were then dispatched to see the identified mothers. Those who met the inclusion criteria were asked to complete consent forms and recruited. The enrolled pregnant women were followed up to birth, and postnatally to 28 days. After birth, the same recruiters informed the study team, who in turn visited the mother-infant dyads at birth, for delivery questionnaire administration, and anthropometric measurements. The maternal vital signs and neonatal anthropometrics (birthweight, length, head, chest and abdominal circumferences), and blood glucose were done within two days of postnatal life (Figure 6). The weighing scales and length/height boards were calibrated before each field visit, and before each measurement was taken. The weighing scales were checked for accuracy daily, with known standard weights. Data was collected using standardized pre-coded questionnaires in ODK, and immediately sent to the server for safe custody by the data manager. Data cleaning and checking for completeness were done for quality control, throughout the data collection process. The principal investigator (BO) worked with and supervised the research assistants, on data collection and documentation.

A total of four research nurses and midwives were trained on the NBS tool. The overall intra-rater (percentage agreement: 82.56%, kappa: 0.806, 95% CI: 0.788 – 0.823) and inter-rater (percentage agreement: 77.5%; kappa: 0.774, 95% CI: 0.613 – 0.936) reliability for the Ballard scoring tool were strong. The principal investigator (BO) worked with and supervised the research assistants on data collection and documentation.

In Paper IV, eighty-six frontline skilled birth attendants (SBAs) were randomized into the intervention and control arms, discussed in the subsequent sections. The randomisation and allocation concealment were done by an independent statistician not part of the trial. The PI was blinded until one week to the trial when she had to plan for the training arms. The RAs were however blinded throughout the trial.

### *Description of intervention*

The control arm received standard HBB training alone, while the intervention group received the standard HBB training and video-debriefing.

***Figure 6. Research assistant taking maternal and neonatal vital signs.***

### *Description of intervention*

The control arm received standard HBB training alone, while the intervention group received the standard HBB training and video-debriefing.

**The control (standard HBB training) arm**

For two days, international, national and regional HBB facilitators trained the SBAs using the 2nd edition of the AAP HBB training curriculum. On Day One of the training, all SBAs undertook pre-test knowledge and skills assessments in the following order: MCQs, BMV, OSCE-A and OSCE B. After the pre-tests, the facilitators gave integrated lectures and demonstrations on neonatal resuscitation skills. The topics covered during the training were: 1) the current global status of newborn health including the burden of neonatal morbidity and mortality, 2) birth preparedness in the labour suit, and 3) care of the healthy, sick and very sick newborns, who require resuscitation and/or referral care. Question and answer (Q&A) sessions followed the lectures.

The facilitators then divided the SBAs into 3 groups of 6-8 participants and undertook further practical demonstrations and group practice of birth preparedness, ventilation skills, and care of healthy and sick newborns. We allowed a total of six hours (three hours on each day) for skills practice. Each group spent 2 hours in each of the three skills sessions. During the different practical sessions, time was given for group practice in threes (a birth attendant, a mother and an assistant). The participants could ask the trainers and PI questions and clarifications on some of the more difficult practical skills techniques.

On Day Two, after all the SBAs were satisfied with the acquired resuscitation skills techniques, post-test assessments were given in a similar way as the pre-tests. At the end of each training day, the participants assessed the ongoing training using the Kirkpatrick training assessment tool. This was to help the training team improve the quality of training and maximize learning.[140]

**Intervention arm (standard HBB training with video debriefing)**

In addition to the standard HBB training, the intervention arm had their HBB simulation sessions video-recorded and used for debriefing. Facilitators divided the participants into two groups. One group remained in the video debriefing session, while the other went for practical skills sessions, as described in the control arm above.

Prior to the debriefing, the participants were asked to set learning objectives at the beginning of each practical session, using the SHARP (Set learning objectives, How it went, Address concerns, Review learning points, Plan ahead) debriefing tool.[141] At the end of each practice session, the lead facilitator asked the SBAs how it went, and addressed concerns arising from the practice session. In addition, the participating team reviewed learning objectives, and planned for improved performance. Viewing of the simulated video recording by the group then followed. The three participants gave feedback and learning points from the simulated case scenario, followed by the rest of the group members and finally, the facilitator. After watching the video, the next team of three had their practice sessions. During each session, the facilitator read the case scenarios aloud and the participating team simulated while being video-graphed. The facilitator repeated the simulated case scenarios, until every participant had had his/her turn to be a birth attendant. The objective assessment of debriefing (OSAD) tool guided the facilitators during debriefing sessions.[141] Two facilitators conducted the debriefing with participants in a separate room from the HBB skills training rooms. As in the control arm, all the participants in the intervention group were encouraged to practice, while asking the facilitators questions and seeking clarification. Finally, the facilitators administered post-test knowledge and skills assessment to the SBAs in the same order, as described in the control group.

## 4.6 Data collection, management and quality control

Data was collected using standardized pre-coded questionnaires in ODK, and immediately sent to the server for safe custody (Papers I – III). The Ballard Scores were done within 7 days for accurate determination of gestational age. A total of four research nurses and midwives were trained on the NBS tool. The overall intra-rater (percentage agreement: 82.6%, kappa: 0.806, 95% CI: 0.788 – 0.823) and inter-rater (percentage agreement: 77.5%; kappa: 0.774, 95% CI: 0.613 – 0.936) reliability for the Ballard scoring tool were strong. The principal investigator (BO) worked with and supervised the research assistants on data collection and documentation. The tarred seca weighing scales were calibrated before each field visit and measurement. The weighing scales were checked for accuracy daily, with known standard weights. The seca length boards were also checked daily for accuracy and those with damage were replaced. The PI worked with and supervised the research assistants on data collection and documentation. Trained midwives and nurses administered the New Ballard Scores.

In Paper IV, research assistants were trained, and the instruments pre-tested. The HBB trainers were nationally trained facilitators. The PI and research assistants were also trained in neonatal resuscitation, assessment methods, and debriefing by a master trainer from Sachs' Children and Youth Hospital, Stockholm, Sweden. Both internal and external validity, and reliability of the OSCE scores were checked by the PI, who participated in a few of the skills sessions, while making independent observations (Figure 7).

***Figure 7. HBB training skills assessment.***

## 4.7 Statistical design and analysis

For all papers, the data were transferred to Stata 14 (Stata Corp, College Station, Texas, US) for analysis.

In Paper I, the incidence of LBW and PB were sex standardized and cluster adjusted and presented as the proportion of LBW and PBs to the total number of live births reported in percent. Descriptive statistics for categorical variables were summarized into proportions and the results presented in Tables 3 and 4 (Pages 10 – 11 in the manuscript). Inferential statistics (the risk factors for LBW and PB), were analysed using bivariable and multivariable generalised estimation equation for the binary categorical outcome of LBW and PB (Tables 3 and 4 above). Significant factors with p value ≤0.05 at bivariable analysis were taken into the multivariable generalized estimation equation model with a log link to Poisson family, adjusting for clustering and potential confounding. Known risk factors for LBW and PB such as infant sex, wealth index, and integrated intervention were also added into the final model even though they were not significantly associated with outcomes at bivariable analysis. The crude and adjusted risk ratios were compared during the multivariable regression analysis. A difference of ≥ 10% between crude and adjusted risk ratios were considered confounding.

In Paper II, descriptive statistics for categorical variables were summarized into proportions, Table 1 (Page 10 in the manuscript). The proportion of neonatal death, hospitalisation, and severe outcomes were sex- and cluster-adjusted and presented as the number of each outcome measures (events), divided by the total number of live births reported per 1,000 live-born infants Table 3. The association between LBW and PB with neonatal death, hospitalisation and severe outcomes were analysed using bivariable and multivariable generalised estimation equation (GEE), for the binary categorical outcomes of death, hospitalisation and severe outcomes and presented in Tables 4, and 5. Significant factors with p value ≤0.05 at bivariable analysis were taken into the multivariable GEE model, with a log link to Poisson family, adjusting for clustering and potential confounding. Known risk factors for neonatal death, hospitalisation and severe outcomes such as wealth index, and integrated intervention combinations, were also added into the final regression model even if they were not significantly associated with the adverse neonatal outcomes. The crude and adjusted risk ratios were compared during the multivariable regression analysis. A difference of ≥10% between crude and adjusted risk ratios were considered confounding.

In Paper III, We analysed a subset of infants with blood glucose measurements and summarized categorical variables as proportions and continuous variables as means (SD) or medians (IQR) and compared them using Student's t tests or Mann-Whitney U tests as appropriate. The results were published in a peer reviewed journal.[142] The prevalence of neonatal hypoglycaemia was defined as the proportion of infants with random blood glucose <47 mg/dl to the total number infants with blood glucose at risk of hypoglycaemia. We used linearized variance estimation adjusting for clustering, to compute the confidence intervals around the estimates. To determine the factors associated with neonatal hypoglycaemia, a multivariable linear regression mixed-effects model was used, in which the random effect was the cluster. Based on scientific literature and biological plausibility, the following covariates were added to the fixed effects part of the model, LBW, delayed breastfeeding initiation, bathing of the baby in the first 24 hours, maternal hyperglycaemia (blood glucose ≥198 mg/dl), any maternal complication during birth, maternal age, maternal education, parity, place of birth, wealth index, and caesarean section. Since this study was nested in a cluster randomized controlled trial, the trial arm was added as a fixed effect. We assumed an exchangeable correlation, and used maximum likelihood estimation in fitting the model. All analyses were done using Stata 14.0.

We also analysed a subset of 1279 infants without missing blood glucose measurements, birthweight and gestational age, to study the effect of small newborns (LBW and PB) on neonatal hypoglycaemia. Then we estimated the effect of neonatal hypoglycaemia on neonatal death, hospitalisation, and severe outcomes (deaths and/or hospitalisation), using multivariable GEE equation with a log link to Poisson family adjusting, for clustering and confounding. The results are also summarized in Tables 6 and 7.

In Paper IV, the data were collected using standardized HBB knowledge (MCQ) and skills (BMV and OSCE-A & B) assessment tools. The data were entered using EPI Data 3.1 (EpiData Association; Enghavevej 34, DK5230 Odense M, Denmark) and exported to Stata Version 14 (StataCorp; College Station, TX, USA) for analysis. Intention to treat analysis was done. At bivariable analysis, baseline categorical variables were summarized into proportions. Chi-squared tests were used in bivariable analysis, to screen for significant differences in baseline SBAs' socio-demographic and HF characteristics between intervention and control arms.

Continuous variables were summarized as means with standard error. The mean differences between the two arms (intervention and control) were compared using two sample t tests. The years in service and monthly number of resuscitations conducted which had *P*-value <0.10 at baseline bivariable analysis, were included in the multi-level mixed effects linear regression model, in order to control for differences in baseline characteristics, clustering and repeated measurements from the same SBAs over time. Stratified analysis and adjustment in multivariable analysis for confounding were carried out. A factor was deemed confounding if 1) the crude and adjusted mean difference in scores differed by $\geq$10%, and/or 2) the crude mean difference was outside the strata specific mean difference ranges or known *a priori* (sex, age, and prior HBB training). The fixed and random effects were intervention and health facility clusters respectively.

## 4.8 Ethical considerations

Ethical clearance was obtained from Makerere University School of Medicine Research and Ethics Committee (SOMREC no. 2015/085), the Uganda National Council for Science and Technology (UNCST no. HS 2478) and REK Vest in Norway (No. 2018/58/REK Vest). Permission was obtained from the district and health facility administrations. The study was also registered with ClinicalTrial.gov NCT02605369). Written informed consents were obtained from all Survival Pluss study participants. Participant confidentiality was maintained, through use of password protected mobile phones and computers.

In addition to the above ethical clearance, permission to conduct the HBB intervention study was obtained from the Ministry of Health through Lira District Health Office and health facility administrations. Assessment was done by the Norwegian Regional Committee for Medical and Health Research Ethics (REK Vest). The HBB study was found to be outside their jurisdiction, and hence qualified for exemption (2018/58/REK Vest). The study was also registered at ClinicalTrials.gov (NCT03703622). Written informed consent was obtained from all the trial SBAs. Informed consent was also obtained from the participants before the video recording. SBAs were not at risk, since we used simulation-based clinical case scenarios. For fairness of participation, we included SBAs from both public and private delivery facilities, and from all HFs providing delivery and newborn care. Training frontline service providers (SBAs) ensured the provision of quality delivery and newborn care, to reduce neonatal mortality in the region. This thesis was prepared in accordance with CONSORT guidelines.[143,144]

# 5. Summary of results

## 5.1 Profile of study participants

Of the 1877 pregnant mothers recruited, 1556 had birthweight, 1416 had blood glucose measurement done, and 1279 had a complete set of blood glucose, birthweight and gestational age by NBS. These are the samples used to for Papers I – III in this thesis, Figure 8.

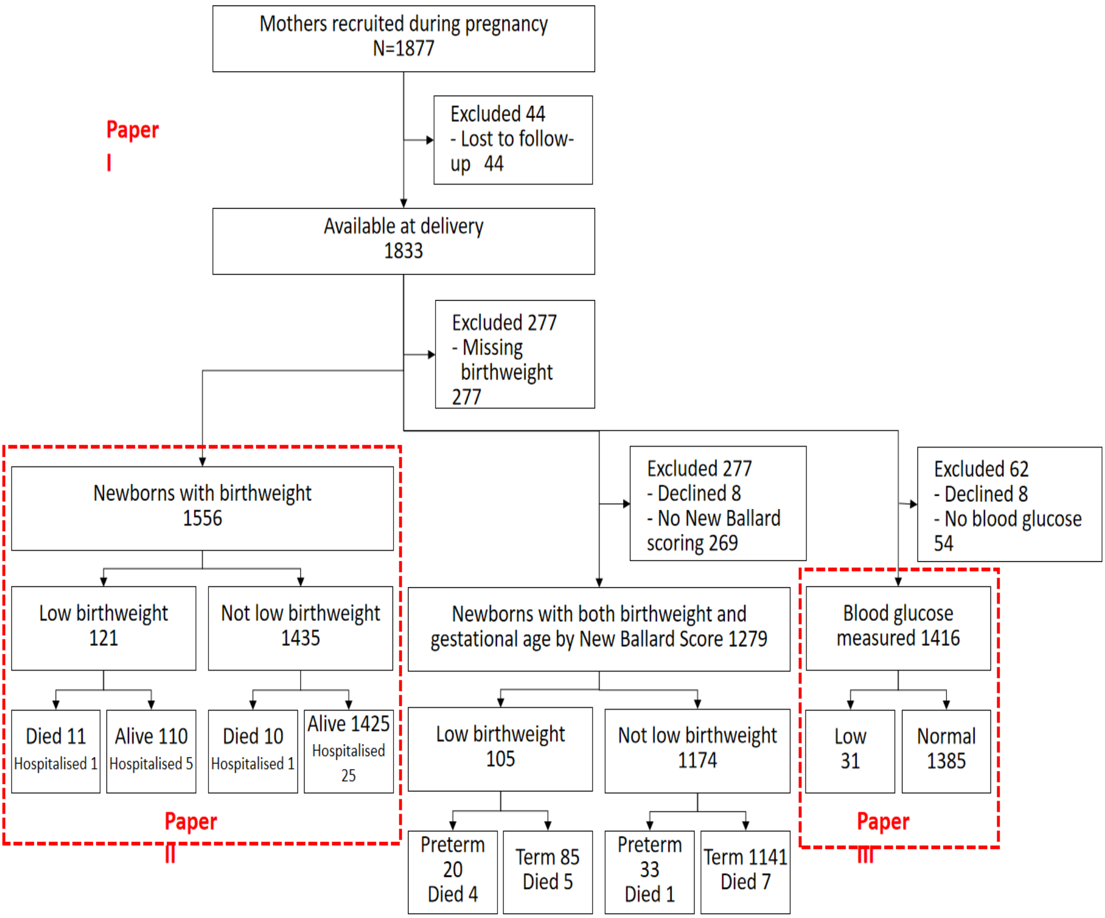



***Figure 8. Study profile for papers I – III.***

Ninety-six health workers from 26 health facility clusters randomized into intervention and control arms, in a ratio of 1:1. A total of 86 were trained, and 81 completed their follow-up at six months. No cluster was lost to follow-up, Figure 9.

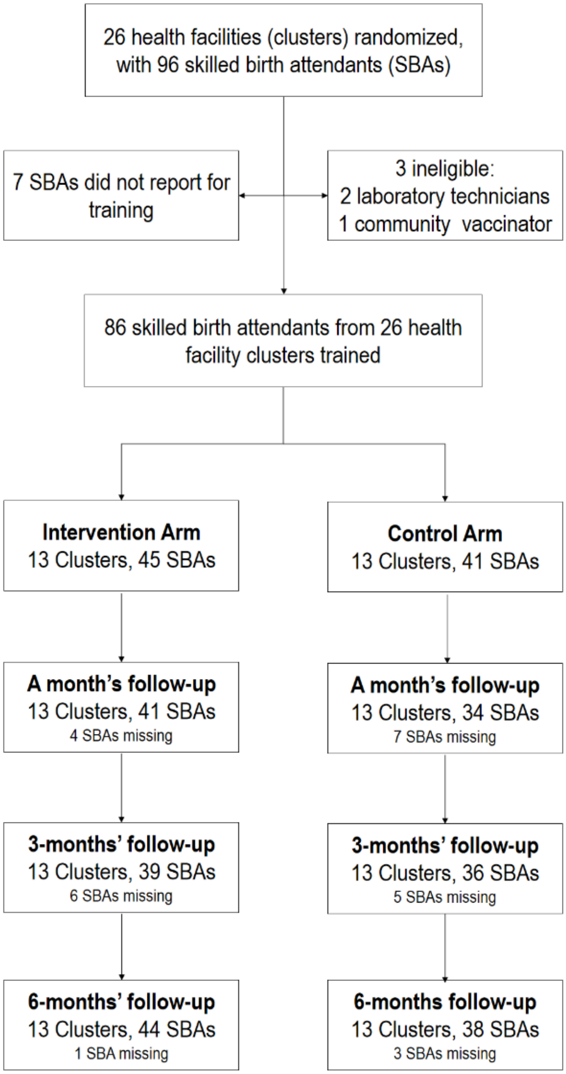



***Figure 9. Consort diagram for the trial in Paper IV.***

## 5.2 Baseline characteristics of study participants

We were able to obtain birthweight of 1556 out of 1877 birthing mothers, 85% of the total. Of these, 1480 (78.9%) were recruited at 28 weeks of gestational age by last menstrual period. Of the 1877 mother-infant dyads, 1556 had birthweight measured within 48 hours after birth, this sample was used to assess LBW incidence and its risk factors. Of the 1556 mother-infant dyads, 1279 had in addition gestational age estimation done within 7 days after birth using the New Ballard Score (NBS), this sample was used to assess PB incidence and its risk factors. Of the 1556 mother-infant dyads, a quarter of the mothers were first time mothers (prime gravida), 22 (1.4%) were twins, and 90% of the mothers were married. Most of the fathers were subsistence farmers. Most families used tap or borehole water for domestic consumption. Around 5% of the mothers were HIV seropositive, while up to 2% did not know their HIV status. Close to 14% of mothers had prior history of small newborn (LBW and (/or PB) in the most recent (second last) delivery. The male to female ratio approximated 1:1, Table 1 in Paper I (Page 8 of the manuscript).

## 5.3 Incidence and risk factors for LBW and PB

The first study explored the incidence and risk factors for low birthweight and preterm birth in post-conflict Northern Uganda (Paper I).

### 5.3.1 The incidence of small newborns (LBW and PB)

*Low birthweight*

An estimated 121 or 7.3% (95% Confidence interval (CI): 5.4% – 9.6%) of the 1556 infants with birthweight had LBW in a post-conflict Northern Uganda.

*Preterm birth*

An estimated (unadjusted) 4.1% (95% CI: 3.1% – 5.4%) of the 1279 infants were born preterm. A sensitivity analysis for different maturity rating total scores (MRTS) cut-offs, if we overestimated the PB by 1-, 2-, 3- or 4- points, are summarized on Table 2 in Paper I (Page 9 of the manuscript). The Ugandan PB estimates by the global burden of disease research group is approximated at minus 3 MRTS. This means we might have overestimated the gestational ages by three MRTS (1.2 weeks or 8.4 days) if the GBD modelled estimates are correct. Further analysis of the data set excluding mothers recruited at 37 or more weeks of gestation, yielded an incidence proportion of 4.0% (95% CI: 3.0 – 5.4) of the 1234 mothers, a similar result as the cohort finding above. Similarly, we also explored the PB estimates by history of preterm birth in prior pregnancy and obtained a prevalence of 4.1% (95% CI: 2.0% – 8.4%) of the 938 non-prime gravida mothers.

### *Small newborns (LBW and/ or PB)*

Of the 1279 infants, 10.8% (95% CI: 8.9 – 13.0) were born either LBW or PB (small newborns) and 20 or 1.6% (95% CI: 1.0 – 2.4) were both preterm and low birthweight in our cohort.

## 5.3.2 Risk factors for small newborns (LBW and PB)

### *Low birthweight*

The factors that were associated with increased risk of a low birthweight infant in our cohort were advanced maternal age (≥35 years), history of a small newborn in prior pregnancy, malaria infection, and unknown malaria status in pregnancy, Table 3 in Paper I (Page 10 of the manuscript). Infants born to mothers aged 35 or more years had almost double (adjusted RR 1.9 (95% CI: 1.1 –3.9) risk of LBW compared to those born to mothers aged 20–34 years. History of a small newborn in the second last pregnancy doubled the risk (aRR: 2.1, 95% CI: 1.2 – 3.9) of LBW compared to those without. A positive malaria test (aRR: 1.7, 95% CI: 1.01–2.9) or an unknown malaria status during pregnancy (aRR 1.9, 95% CI: 1.1 – 3.2) almost doubled the risk of LBW among the infants compared to those with known malaria negative tests. On the other hand, infants whose mothers received intermittent preventive treatment for malaria during pregnancy had a 40% (95% CI: 20% – 60%) reduced risk of being LBW compared to those who did not. The integrated intervention package had no effect on the LBW in this post-conflict setting of northern Uganda. Similarly, other known risk factors for LBW such as poverty, maternal education, teenage motherhood, grand multi–parity, ANC attendance and HIV infection were not associated with increased risks of LBW among mothers in the cohort. These and more details are summarized in Table 3 in Paper I.

### *Preterm birth*

HIV infection was associated with an increased risk of PB (adjusted RR: 2.9, 95% CI: 1.1 – 7.3) in the multivariable analysis. Maternal education (≥7 years) was associated with a reduced risk of PB (adjusted RR: 0.3, 95% CI: 0.1 – 0.98). More details are summarised in Table 4 in Paper I (Page 11 of the manuscript).

## 5.4 LBW (and PB) as risk factors for neonatal death and/or hospitalisation

In Paper II, we assessed 1) the proportion of neonatal death and/or hospitalisation among small newborns and 2) the subsequent effect of LBW and/or PB (small newborns) on neonatal death and/or hospitalisation.

Table 4. Numbers and adjusted rates of neonatal death, hospitalisations and severe outcomes.

| | **LBW infants n=121** | **Non-LBW infants n=1435** | **All infants N=1566** | **Preterm (PB) N=53** | **Non-PB N=1226** | **All N=1279** |
|---|---|---|---|---|---|---|
| Neonatal deaths (number) | 11 | 10 | 21 | 5 | 12 | 17 |
| Neonatal mortality/ 1000 live births (95% CI) | 103 (47.2 – 212) | 5.4 (2.1 – 13.9) | 12.5 (6.9 – 22.6) | 90.9 (25.6 – 275) | 6.4 (1.9 – 21.1) | 10.6 (4.7 – 23.7) |
| Neonatal hospitalisations (number) | 6 | 26 | 32 | 2 | 20 | 22 |
| Hospitalisation rate/ 1000 live births (95% CI) | 86.2 (34.1 – 201) | 14.9 (7.6 – 28.9) | 20.1 (11 – 34) | 30.3 (3.7 – 208) | 14.4 (7.1 – 29.1) | 15.2 (7.9 – 29.1) |
| Neonatal 'severe outcomes' (=no of deaths or hospitalisations) | 16 | 35 | 51 | 6 | 32 | 38 |
| Neonatal 'severe outcomes' rate/ 1000 live births (95% CI) | 172 (99 – 283) | 2.0 (11 – 35) | 31.1 (20 – 48) | 121 (41 – 308) | 20.8 (9.8 – 43) | 25.8 (14 – 46) |

*CI confidence interval*

### 5.4.1 The proportion of neonatal death and/or hospitalisation

The adjusted risk of death, hospitalisation and severe outcomes among LBW and PBs are summarised in Table 4.

### 5.4.2 LBW and PB as risk factors for neonatal death, hospitalisation and severe outcomes

*Low birthweight*

**Neonatal death**

The overall proportion of neonatal death was: 21/1556 or 13.5 (95% CI: 8.8 – 20.6) per 1000 live births. The adjusted proportion of neonatal death among LBW infants were 103 (95% CI: 47.2 – 212) per 1000 live births. Compared to normal birthweight, LBW was associated with an increased risk of neonatal death (adjusted risk ratio, aRR: 7.6, 95% CI: 4.0 – 15). On the other hand, early initiation of breastfeeding (aRR: 0.2, 95% CI: 0.1 – 0.8) and the domestic use of tap/borehole (aRR: 0.2, 95% CI: 0.1 – 0.5) water were associated with reduced risk of neonatal death. More details are in Tables 5.

Table 5. LBW as risk for neonatal death among infants in northern Uganda.

| Characteristics | All N=1556 n (%) | Died N=21 n (%) | Crude RR (95% CI) N=1556 | p value for crude RR | Adjusted RR (95% CI) N=1556 |
|---|---|---|---|---|---|
| **Primary exposure** | | | | | |
| *Birthweight* | | | | | |
| Normal birthweight | 1435 (92.2) | 10 (47.6) | Ref | | Ref |
| Low birthweight | 121 ( 7.8) | 11 (52.4) | 13 (6.6 – 25) | 0.000 | **7.6 (4.0 – 15)** |
| **Maternal characteristics** | | | | | |
| *Maternal age* | | | | | |
| 12-19 years | 415 (26.7) | 10 (47.6) | 2.9 (1.1 – 7.8) | 0.025 | 1.8 (0.6 – 5.1) |
| 20-34 years | 982 (63.1) | 8 (38.1) | Ref | | Ref |
| ≥35 years | 159 (10.2) | 3 (14.3) | 2.3 (0.5 – 11) | 0.293 | 1.2 (0.5 – 3.0) |
| *Maternal education* | | | | | |
| 0-6 years | 1246 (80.1) | 17 (81.0) | Ref | | |
| ≥7 years | 310 (19.9) | 4 (19.1) | 0.9 (0.4 – 2.5) | 0.902 | |
| *Maternal vocational education* | | | | | |
| No | 1371 (88.1) | 15 (71.4) | Ref | | Ref |
| Yes | 185 (11.9) | 6 (28.6) | 3.0 (1.5 – 5.9) | 0.002 | 1.6 (0.6 – 4.2) |
| *Marital status* | | | | | |
| Married | 1417 (91.1) | 19 (90.5) | 1.0 (0.3 – 3.2) | | |
| Single/separated/ divorced/widow | 139 ( 8.9) | 2 ( 9.5) | Ref | | |
| *Wealth index* | | | | | |
| Lower 40% | 708 (45.5) | 9 (42.9) | Ref | | Ref |
| Middle 40% | 547 (35.2) | 7 (33.3) | 1.0 (0.4 – 2.7) | 0.984 | 1.8 (0.8 – 3.6) |
| Upper 20% | 301 (19.3) | 5 (23.8) | 1.3 (0.4 – 4.0) | 0.652 | 2.2 (0.9 – 5.1) |
| *Father's occupation* | | | | | |
| Farmer | 1058 (68.0) | 13 (61.9) | 1.0 (0.3 – 3.0) | 0.942 | |
| Employed | 348 (22.4) | 6 (28.6) | 1.3 (0.3 – 6.4) | 0.731 | |
| Unemployed | 150 ( 9.6) | 2 ( 9.5) | Ref | | |
| *Domestic water source* | | | | | |
| Tap/Borehole | 977 (62.8) | 5 (23.8) | 0.2 (0.1 – 0.5) | 0.001 | **0.2 (0.1 – 0.5)** |

| | | | | | |
|---|---|---|---|---|---|
| Spring/river/well /stream/pond | 579 (37.2) | 16 (76.2) | Ref | | Ref |
| *Intervention* | | | | | |
| No | 740 (47.6) | 12 (57.1) | Ref | | Ref |
| Yes | 816 (52.4) | 9 (42.9) | 0.7 (0.3 – 1.8) | 0.418 | 0.7 (0.3 – 1.5) |
| **Maternal clinical characteristics** | | | | | |
| *Facility delivery* | | | | | |
| No | 482 (31.1) | 7 (33.3) | Ref | | |
| Yes | 1070 (68.9) | 14 (66.7) | 0.9 (0.3 – 2.4) | 0.819 | |
| *History of a small newborn* | | | | | |
| No | 985 (63.3) | 12 (57.1) | Ref | | |
| Yes | 218 (14.0) | 3 (14.3) | 1.1 (0.2 – 6.2) | 0.909 | |
| Prime gravida | 353 (22.7) | 6 (28.5) | 1.4 (0.5 – 4.2) | 0.554 | |
| *Parity* | | | | | |
| Prime Gravida | 353 (22.7) | 6 (28.6) | 1.4 (0.5 – 3.8) | 0.547 | |
| 1-6 | 1043 (67.0) | 13 (61.9) | Ref | | |
| 7 or more | 160 (10.3) | 2 ( 9.5) | 1.0 (0.2 – 4.7) | 0.988 | |
| *HIV[a] infection* | | | | | |
| No | 1455 (93.5) | 19 (90.5) | Ref | | |
| Yes | 73 ( 4.7) | 1 ( 4.7) | 1.0 (0.1 – 8.8) | 0.965 | |
| Unknown | 28 ( 1.8) | 1 ( 4.8) | 2.7 (0.3 – 23) | 0.354 | |
| *Antenatal attendance* | | | | | |
| No | 352 (22.6) | 3 (14.3) | Ref | | |
| Yes | 1204 (77.4) | 18 (85.7) | 1.7 (0.6 – 5.0) | 0.319 | |
| *IPT[b] for malaria in pregnancy* | | | | | |
| No | 704 (45.2) | 10 (47.6) | Ref | | |
| Yes | 852 (54.8) | 11 (52.4) | 0.9 (0.4 – 2.1) | 0.831 | |
| *Malaria in pregnancy* | | | | | |
| No | 502 (32.3) | 4 (19.0) | Ref | | Ref |
| Yes | 388 (24.9) | 3 (14.3) | 0.9 (0.2 – 3.7) | 0.937 | 1.3 (0.3 – 6.3) |
| Unknown | 666 (42.8) | 14 (66.7) | 2.7 (0.7 – 10) | 0.160 | 2.4 (0.8 – 6.9) |
| **Infant characteristics** | | | | | |
| *Infant sex* | | | | | |
| Female | 757 (48.7) | 11 (52.4) | Ref | | |
| Male | 799 (51.3) | 10 (47.6) | 0.9 (0.4 – 2.0) | 0.742 | |
| *Delayed or no birth cry* | | | | | |
| No | 1489 (95.7) | 15 (71.4) | Ref | | Ref |
| Yes | 67 ( 4.3) | 6 (28.6) | 8.9 (3.2 – 24) | 0.000 | 2.1 (0.4 – 9.9) |
| *Breastfeeding initiation* | | | | | |
| No | 39 ( 3.0) | 6 (28.6) | Ref | | Ref |
| Yes | 1517 (97.7) | 15 (71.4) | 0.1 (0.03 – 0.2) | 0.000 | **0.2 (0.1 – 0.8)** |
| *Postpartum infant bath* | | | | | |
| No | 618 (39.7) | 14 (66.7) | Ref | | Ref |
| Yes | 938 (60.3) | 7 (33.3) | 0.3 (0.2 – 0.7) | 0.002 | 0.6 (0.3 – 1.2) |

*[a] human immunodeficiency syndrome, [b] intermittent preventive treatment for malaria, significant adjusted risk ratios in bold*

## Hospitalisation

Compared to normal birthweight, LBW was associated with an increased risk of neonatal hospitalisation (aRR: 2.8; 95% CI: 1.1 – 7.5). In addition, compared to mothers aged 20 – 34 years, teenagers were at an increased risk of neonatal hospitalisation (aRR: 2.1, 95% CI: 1.1 – 4.2). These and more are in Table 4 in Paper II (Page 13 of the manuscript).

### *Severe outcomes*

Compared to normal birthweight, LBW was associated with an increased risk of severe outcomes (aRR: 4.4, 95% CI: 2.7 – 7.2). Other factors associated with neonatal severe outcomes were: teenage motherhood, delayed birth cry, early initiation of breastfeeding, and use of borehole or tap water for domestic consumption. Teenage mothers were twice as likely to have severely ill (aRR: 1.8, 95% CI: 1.1 – 2.9) infants compared to mothers aged 20 – 34 years. Infants with delayed or no birth cry (aRR: 2.3, 95% CI: 1.05 – 5.2) were at more risk of severe outcomes, than those without. On the other hand, early initiation of breastfeeding reduced the risks of severe outcomes (aRR: 0.4, 95% CI: 0.2 – 0.8). Similarly, the domestic use of tap/borehole water was associated with a decreased risk of severe outcomes (aRR: 0.4, 95% CI: 0.3 – 0.7) in the neonatal period. More details in Table 5 in Paper II (Page 15 of the manuscript).

### *Preterm birth*

Similarly, PB was associated with increased risk of neonatal death, hospitalisation and severe outcomes, Table 6.

## 5.5 Neonatal hypoglycaemia: burden and outcomes

In Paper III, we explored the prevalence and factors associated with neonatal hypoglycaemia among infants with blood glucose records as a whole,[142] and then among those with no missing birthweight and gestational age estimated by the NBS (presented in the thesis).

### 5.5.1 Prevalence of neonatal hypoglycaemia

The mean neonatal blood glucose level was 81.6 mg/dl (SD 16.8), and the median blood glucose 81.0 (IQR 70.2, 93.6). The prevalence of neonatal hypoglycaemia was 2.2% (31/1416): 95% CI 1.2%, 3.9%.[142] When we restricted the analysis to 1279

Table 6. PB as a risk factor neonatal death and/or hospitalisation.

| **Factors** | **Deaths Adj. RR [95% CI] N=1279** | **Hospitalisation Adj. RR [95% CI] N=1279** | **Severe outcomes Adj. RR [95% CI] N=1279** |
|---|---|---|---|
| **Primary exposure** | | | |
| *Gestational age* | | | |
| Term | Reference | Reference | Reference |
| Preterm | **6.4 (1.7 – 24)** | 2.1 (0.6 – 7.9) | **3.1 (1.3 – 7.6)** |
| **Maternal socio-demographic characteristics** | | | |
| *Maternal age in years* | | | |
| 12 – 19 | 1.7 (0.6 – 5.1) | 1.8 (0.7 – 4.4) | **1.7 (1.01 – 3.0)** |
| 20 – 34 | Reference | Reference | Reference |
| 35 – 49 | 2.4 (0.7 – 8.1) | 2.6 (0.8 – 8.3) | 2.3 (1.0 – 5.7) |
| *Maternal education* | | | |
| 0 – 6 years | Reference | Reference | |
| ≥7 years | | 0.5 (0.1 – 1.9) | |
| *Wealth index groups* | | | |
| *Lower 40%* | Reference | Reference | Reference |
| Middle 40% | 0.8 (0.2 – 2.9) | 0.7 (0.3 – 1.9) | 0.8 (0.4 – 1.9) |
| Upper 20% | 1.5 (0.6 – 4.2) | 1.6 (0.7 – 8.3) | 1.4 (0.7 – 2.8) |
| *Domestic water source* | | | |
| Spring/river/well/stream/pond | Reference | Reference | Reference |
| Tap | 0.2 (0.1 – 0.5) | 0.6 (0.3 – 1.2) | 0.4 (0.2 – 0.7) |
| *Intervention* | | | |
| No | Reference | Reference | Reference |
| Yes | 0.5 (0.7 – 15) | 0.7 (0.3 – 1.4) | 0.7 (0.4 – 1.3) |
| **Maternal clinical characteristics** | | | |
| *Malaria in pregnancy* | | | |
| Negative | Reference | Reference | |
| Positive | 2.5 (0.7 – 9.0) | 0.7 (0.2 – 2.5) | |
| Unknown | 4.5 (1.5 – 14) | 0.5 (0.2 – 1.4) | |
| **Infant factors** | | | |
| *Delayed or no birth cry* | | | |
| No | Reference | | Reference |
| Yes | 3.4 (0.7 – 15) | | **2.4 (1.1 – 5.6)** |
| *Breastfeeding initiation* | | | |
| No | Reference | | Reference |
| Yes | 0.2 (0.03 -1.0) | | **0.3 (0.2 – 0.7)** |
| *Postpartum infant bath* | | | |
| No | Reference | Reference | |
| Yes | 0.9 (0.3 – 2.6) | **0.3 (0.1 – 0.8)** | |

*CI confidence interval, significant adjusted risk ratios in bold*

infants with blood glucose measurements, gestational age and birthweight, the prevalence of neonatal hypoglycaemia was 2.5% (95% CI: 1.8% – 4.2). The proportion of mothers with the diabetic range random blood glucose of ≥10.1mmo/l was 23/1416 or 1.6% (95% CI: 1.1% – 2.4%).

### 5.5.2 Risk factors for neonatal hypoglycaemia

When the outcome (hypoglycaemia) was analysed on a continuous scale, the risk factors for neonatal hypoglycaemia among the infants were: delayed breastfeeding initiation; postnatal infant bath in the first 24 hours after birth, and the infant age ≤3 days at examination.[142] The Mean blood glucose levels were 2.6 mg/dl lower among infants who were breastfed later than 1 hour, compared to those who were breastfed in the first hour after birth [adjusted mean difference, −2.6; 95% CI: −4.4, −0.79].

Table 7. Risk factors for neonatal hypoglycaemia based on two separate models.

| Factors | Adj. RR [95% CI] N=1279 | Adj. RR [95% CI] N=1556 |
|---|---|---|
| **Primary exposures** | | |
| Preterm birth | | |
| No | | |
| Yes | **3.3 (1.1 – 9.7)** | |
| Low birthweight | | |
| No | | |
| Yes | | **4.8 (2.4 – 9.5)** |
| **Maternal demographics** | | |
| Water source for domestic use | | |
| springs/wells/rivers | Ref | Ref |
| Tap/borehole | 1.7 (0.5 – 5.7) | 1.8 (0.6 – 5.9) |
| Malaria IPT in pregnancy | | |
| No | Ref | Ref |
| Yes | 0.6 (0.3 – 1.1) | 0.6 (0.3 – 1.2) |
| No or delayed birth cry | | |
| No | Ref | Ref |
| Yes | 1.3 (0.3 – 5.2) | 1.0 (0.3 – 4.1) |
| Intervention | | |
| No | Ref | Ref |
| Yes | 1.0 (0.3 – 2.8) | 1.1 (0.4 – 3.2) |

RR risk ratio, CI confidence interval, significant adjusted risk ratios in bold. We fitted separate models each for 1279 PB and 1556 LBW.

Infants who were bathed within 24 hours of life, had an average of 2.3 mg/dl lower glucose concentration than those who were bathed afterwards [adjusted mean −2.3; 95% CI: −0.46, −4.2]. Infants aged ≤3 days old had an average of 12.2 mg/dl lower glucose concentration, than those aged over 3 days [adjusted mean, −12.2; 95% CI:

−14.0, −10.4].[142] More details are in Table 2 Paper III (Page 6 in the article) and Table 7.

As a binary categorical outcome variable, risk factors for neonatal hypoglycaemia were LBW and preterm birth. There was a three-fold (adjusted RR 3.3, 95% CI: 1.2 – 8.9) associated increased risk of neonatal hypoglycaemia among preterm, compared to term infants. Similarly, LBW infants were five times (adjusted RR 4.8, 95% CI: 2.4 – 9.5) at more risk of neonatal hypoglycaemia, than those with normal birthweight, Table 7.

### 5.5.3 Neonatal outcomes associated with hypoglycaemia

Neonatal hypoglycaemia was associated with an increased risk of neonatal death,

Table 8. Neonatal hypoglycaemia as a risk for death and/or hospitalisation.

| **Factors** | **Death Adj. RR [95% CI] N=1279** | **Hospitalisation Adj. RR [95% CI] N=1279** | **Severe outcome Adj. RR [95% CI] N=1279** |
|---|---|---|---|
| **Primary exposure** | | | |
| *Neonatal hypoglycaemia* | | | |
| No | Ref | Ref | |
| Yes | 2.4 ( 0.6 – 101) | **6.3 (2.7 – 14)** | **3.9 (2.1 – 7.2)** |
| **Maternal demographic characteristics** | | | |
| *Maternal age in years* | | | |
| 12 – 19 | 2.3 ( 0.8 – 6.5) | 1.3 (0.5 – 3.4) | 1.9 (1.1 – 3.1) |
| 20 – 34 | Ref | Ref | Ref |
| 35 – 49 | 2.2 ( 0.5 – 8.9) | 2.4 (0.8 – 6.9) | 2.2 (0.9 – 5.3) |
| *Maternal education in years* | | | |
| 0 – 6 | | Ref | |
| 7 or more | | 0.5 (0.1 – 1.8) | |
| *Water source for domestic use* | | | |
| springs/wells/rivers/ponds/streams | Ref | Ref | |
| Tap/borehole | **0.1 (0.05 – 0.4)** | 0.6 (0.3 – 1.1) | **0.4 (0.2 – 0.6)** |
| *Intervention* | | | |
| No | Ref | | Ref |
| Yes | 0.6 ( 0.3 – 1.4) | | 0.8 (0.4 – 1.4) |
| **Infant factors** | | | |
| *No or delayed birth cry* | | | |
| No | Ref | | Ref |
| Yes | 3.1 ( 0.7 – 13) | | 1.9 (0.8 – 5.0) |
| *Initiate breastfeeding* | | | |
| No | Ref | | Ref |
| Yes | **0.1 (0.03 – 0.6)** | | **0.3 (0.1 -0.8)** |
| *Postpartum infant bath* | | | |
| No | Ref | | Ref |
| Yes | **0.8 (0.03 – 0.7)** | | **0.5 (0.3 – 0.7)** |

*RR risk ratio, CI confidence interval, significant adjusted risk ratios in bold* hospitalisation and severe outcomes. The other factors associated with neonatal death and severe outcomes from this model were use of tap/borehole water for domestic use, initiation of breastfeeding, and infant bath, Table 8.

## 5.6 The effects of HBB standard training on SBAs competence attainment and retention

We tested the effect of adding video debriefing to standard HBB training on SBA's knowledge and skills attainment, immediate post-training, and over a six-month follow-up period (Paper IV). The intervention group received video debriefing in addition to standard training, while the control arm received standard training only.

### 5.6.1 The effects of training on knowledge and skills attainment and retention

Adding video debriefing to standard HBB training improved skills, and the combined knowledge and skills (competence) attainment in the immediate (2 days) post-training period, after adjusting for baseline characteristics.[145] Similarly, SBAs in the intervention group were more likely to retain skills and competence over the six-month's follow-up period, in comparison to SBAs in the control group after controlling for confounding and clustering (Table 2 in Paper IV).[145] Analysis of pooled scores over six months also showed higher knowledge, skills and competence scores among SBAs in the intervention, compared to the standard training group, Table 3 in Paper IV (Page 7 in the article).[145]

The number of years of in-service and routine neonatal resuscitation practice are the other factors that affected SBAs knowledge and skills retention. SBAs who resuscitated at least one baby per month, and those who had more than 5 years in service, had less retention of neonatal resuscitation competence during the six-month follow-up period.

### 5.6.2 Trends in knowledge and skills mean scores between intervention arms over time

The overall knowledge and skills mean scores in both intervention and control arms, improved in the immediate (2 days) post-training period. The video debriefing arm maintained higher scores in knowledge and skills throughout the follow-up period. In addition, the mean knowledge scores remained significantly higher than the overall and individual skills components, even at baseline, Figure 10.

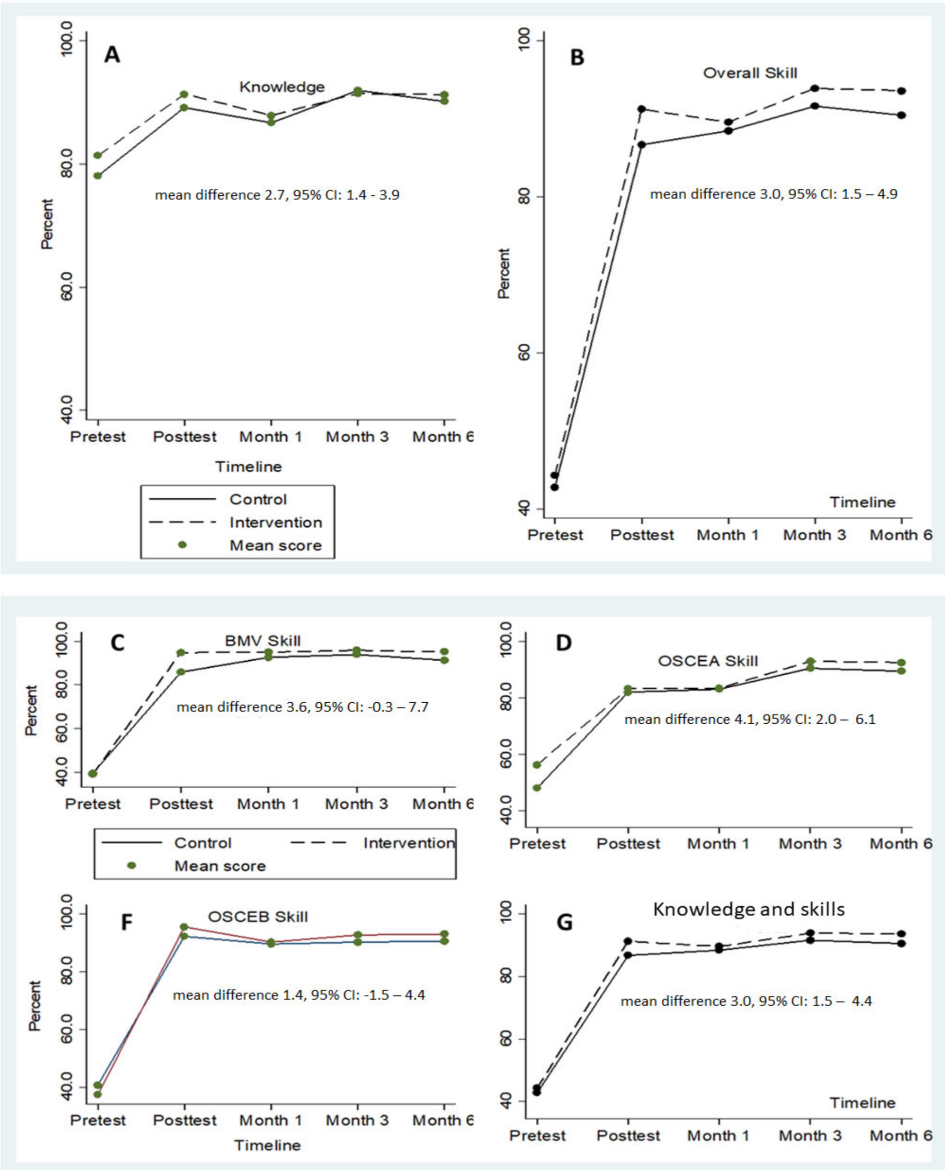



***Figure 10. Knowledge and skills mean scores trends over 6 months.***

# 6. Discussion

This thesis reports the burden, risk factors and outcomes of small newborns [low birthweight (LBW) and preterm birth (PB)], and the prevalence of neonatal hypoglycaemia in post-conflict Northern Uganda. In addition, it examines the effect of a low-cost intervention of standard HBB training with video debriefing on skilled birth attendants' (SBAs) neonatal resuscitation competence attainment and retention, over a 6-month follow-up period. The findings are discussed in the following order:

a) The incidence and risk factors for LBW and PB (small newborns).
b) LBW and PB as risk factors for neonatal death and/or hospitalisation among small newborn infants.
c) The prevalence, factors associated with, and outcomes of neonatal hypoglycaemia.
d) The effect of adding video debriefing to standard HBB training, compared to standard training only on frontline SBAs' competence attainment and retention.

## 6.1 The incidence and risk factors for small newborns

### 6.1.1 Incidence of LBW and PB

#### *Low birthweight (LBW)*

In our cohort, the incidence of LBW 7.3%. The proportion of LBW in our study in this area of Northern Uganda is lower than most other estimates, be it global, sub-Saharan Africa, or Uganda.[146-148] This study was a sub-study of a trial in which one of the inclusion criteria was a gestational age 28 or more weeks of pregnancy. Given that women were enrolled at 28 or more weeks, preterm births occurring before recruitment were systematically excluded. Therefore, our study is likely to have underestimated the true incidence of both LBW and PB (see section 6.5.3)

### Preterm birth

The PB proportion in our cohort was 5.0% and is similar to a hospital-based study in Eastern Uganda, with similar inclusion and exclusion criteria.[23] The observed estimate in this cohort, however, is lower than the global sub-Saharan Africa or Uganda estimates.[22,148]

The low PB proportion observed in our study may be due to the trial eligibility criteria discussed above that could have resulted in exclusion of some preterm births occurring before recruitment into the main trial. Secondly, the NBS for foetal maturation for gestational age determination (instead of mid-pregnancy ultrasound as the gold standard), may have contributed to the underestimation of PB in this cohort. For instance, a study by Sasidharan and colleagues reported that NBS overestimated gestational age (GA) by up to 2 weeks (5 MRTS), with increasing postnatal age.[36] Therefore, if the current global PB modelled estimates by the global burden of disease (GBD) research group are true, we may have over-estimated GA by 3MRTS (1.2 weeks), see our sensitivity analysis in Paper I. Although scientists modified the NBS system to identify extremely preterm babies up to seven days of postnatal age, it seems postnatal age at assessment may have played a role in the PB estimates in our cohort. The exclusion of 363/1833 (19.8%) infants not reached for NBS gestational age (GA) assessment within 7 days of postnatal life, and another 191/1833 (10.4%) of the infants without birthweight, may have also resulted in the observed low PB incidence proportion. Further analyses of two subsets of mothers who had history of preterm birth and those recruited at 28 weeks of gestational age by LMP, yielded similar findings as the entire cohort. This reduced our fear of selection bias to some degree. Despite the challenges faced in PB diagnosis in our setting, the findings may still be relevant in contributing to the pool of knowledge on preterm births and associated risk factors, to guide decision making in a resource-limited post-conflict setting.

### 6.1.2 Risk factors for low birthweight and preterm birth

#### *Risk factors for low birthweight*

Factors associated with low birthweight included maternal age ≥35 years, history of small newborn in the previous pregnancy, maternal malaria in pregnancy and intermittent preventive treatment (IPT) for malaria. The finding that advanced maternal age (≥35 years) was associated with an increased risk of LBW in our cohort is not unique to our report. Numerous studies have described the increased risk of LBW with low or advanced maternal age.[149,150] The study also reports an associated increased risk of LBW among mothers with history of a small newborn, in the most recent pregnancy. Other studies report similar links.[151,152]

The relationship between malaria in pregnancy and its association with increased risk of LBW has been reported elsewhere.[153] Similarly, we also report reduced risk of LBW among infants born to mothers who had intermittent preventive therapy (IPT) for malaria during pregnancy. Malaria IPT during pregnancy reduces placental malaria, a long known risk factor for LBW and preterm births (small newborn).[154]

#### *Risk factors for preterm birth*

Factors associated with and increased risk of preterm birth include maternal HIV infection. Maternal education for seven or more years was associated with a reduced risk. Our finding that low maternal education is associated with an increased risk of PB has been reported elsewhere.[155-157] The increased risk of PBs among HIV infected women, compared to the uninfected has also been known over the last 3 decades.[158]

In our cohort, teenage motherhood doubled the risk of PB and this is of public health importance. The finding is similar to results of several other studies across the globe.[159,160] Although the biological link between teenage pregnancy and PB is not properly understood,[161,162] pregnant teens are likely to be disfavoured in several aspects such as education, access to care and nutrition compared to older mothers.[163-165]

The study also reported an increased risk of PB among male infants, compared to female infants. This may be a methodological artefact due to differences in NBS scoring of the two sexes. An analysis of mean difference for the overall MRTS and individual elements for physical and neuromuscular scores by sex, demonstrated a difference in physical maturity rating for breasts. Female infants were systematically over-scored by 0.14 (0.08 – 0.21) points in the physical maturity rating for breasts, which may contribute to fewer infants being classified as being PB. It is still possible that there is still true increase in the risk of PB for male infants as this has been reported elsewhere.[166,167]

## 6.2 Small newborn as a risk factor for adverse neonatal outcomes

### 6.2.1 Low birthweight as a risk for adverse neonatal outcomes

In our cohort, the overall neonatal mortality risk in the study population was 12.5/1000 live births, slightly over the SDG 3.2 target of 12 per 1000 live births. But LBW infants were eight times more likely to die compared to non-LBW infants. In fact, half of the neonatal deaths occurred in the LBW group which means that LBW is one of the main drivers for the neonatal mortality. Efforts to reduce the number of LBW infants and/or to prevent adverse outcomes in this vulnerable group may be beneficial substantially reducing neonatal deaths and contribute to the attainment of the SDG target 3.2. The frequency of hospitalisation and 'severe outcomes' (death or hospitalisation) among LBW infants were also higher than among non-LBW infants. According the WHO, LBW is a known risk factor for neonatal mortality and morbidity.[20]

### 6.2.2 Preterm birth as a risk factor for adverse neonatal outcomes

As reported in the results section in our cohort, 94.3 neonatal deaths per 1000 live births occurred among PBs. Compared to term infants, this was a six-fold increase in neonatal death. Efforts to reduce the number of PB infants and/or to prevent adverse outcomes in this group could reduce neonatal morbidity and mortality.

### 6.2.3 Other risk factors for adverse neonatal outcomes

In systematic reviews and meta-analyses, other known risk factors of neonatal death asphyxia and extreme maternal ages including teenage pregnancy, delayed initiation of breastfeeding and water and hygiene.[39,168-172] These factors were also evident in our study.

Whereas being wealthy has been traditionally associated with favourable neonatal outcomes, we report a finding to the contrary.[147,173] This may be a spurious association, because, wealthy mothers may be more likely to seek care for their newborns compared to those in lower wealth groups, even in sub-Saharan Africa.[174]

## 6.3 Prevalence of neonatal hypoglycaemia

This thesis also examined the prevalence and risk factors for neonatal hypoglycaemia with discussion details presented hereunder.

### 6.3.1 The prevalence of neonatal hypoglycaemia

Our finding of a 2.7% (95% CI 1.7% – 4.3%) prevalence of neonatal hypoglycaemia is similar to a 2% nationwide prevalence of impaired fasting glycaemia (IFG) among adults in Uganda.[175] It is also similar to other study findings among infants from America and India.[176,177] Aside from our study, there are no population based estimates for newborns in Uganda. Our findings, however, are lower than those reported elsewhere.[178-181] Possible reasons may explain the lower prevalence of neonatal hypoglycaemia in our cohort. Firstly, different studies used different cut-off thresholds and varying postnatal age.[178,181,182] This lack of consensus on a unified definition of neonatal hypoglycaemia threshold compounds the difficulties in making meaningful comparisons across sites. Secondly, there was a high level of early initiation of, and continued breastfeeding among the study population. Breastfeeding prevents and resolves transitional neonatal hypoglycaemia.[182] Thirdly, the study population had a low proportion of maternal hyperglycaemia with random blood glucose of $\geq$10.1mmol/l ((1.6%, 95% CI: 1.1% – 2.4%), a marker of diabetes mellitus, and a known risk factor for neonatal hypoglycaemia.

### 6.3.2 LBW and PB were associated with increased risks for neonatal hypoglycaemia

This study found an increased risk of neonatal hypoglycaemia amongst LBW and PB infants compared to their respective term and normal birthweight counterparts. The findings has also been described in India.[176] Both LBW and PB are known risk factors for neonatal hypoglycaemia.[180] This is because small birth sized infants are biologically disadvantaged by low or inadequate glycogen stores and increased glucose utilization from hypothermia.[181]

### 6.3.3 Other risk factors for neonatal hypoglycaemia

The finding that delayed breastfeeding initiation is associated with neonatal hypoglycaemia, is not surprising. It has been reported numerous times by other authors that breastfeeding is an initial means of correcting neonatal hypoglycaemia.[182,183] This finding reinforces the need to encourage mothers to breastfeed their infants within the first hour after birth. It also sheds light on a potential mechanism through which delayed breastfeeding may increase the risk of neonatal morbidity and mortality.[184]

Bathing the newborn within 24 hours after birth appears to be associated with neonatal hypoglycaemia. This may be explained by the fact that bathing newborns within 24 hours of birth, predisposes them to cold stress and hypothermia,[185] which are risk factors for neonatal hypoglycaemia.[176] In our study sample however, the association between hypothermia and hypoglycaemia was very weak and imprecise. Neonates aged ≤3 days had lower blood glucose concentrations, compared to those >3 days old. The finding of declining incidence of neonatal hypoglycaemia with increasing postnatal age is not unique.[142,186] This may be due to the resolution of transitional hypoglycaemia with increasing postnatal age.[142,179,181]

### 6.3.4 Neonatal hypoglycaemia and adverse neonatal outcomes

Neonatal hypoglycaemia was associated with an increased risks of neonatal death, hospitalisation and severe outcomes. Historically, neonatal hypoglycaemia has been a known common preventable metabolic condition, with detrimental short-and long-term effects, if left untreated.[181,187] It is also a known risk for neonatal seizures, irritability, brain injury, as well as intractable epilepsy in early chidlhood.[184]

## 6.4 Helping babies breathe (HBB) training

Skill birth attendants (SBAs) trained using standard HBB curriculum with video debriefing, retained neonatal resuscitation knowledge and skills, better than those who only had standard training.[145] Moreover, the SBAs who routinely resuscitated at least one or more neonates per month, were less likely to retain competence than those who did not have real life practice. This is a counter intuitive finding that is difficult to explain. SBAs who had been in service for five or more years, exhibited reduced competence retention during the six-month follow-up period, compared to those who had less than five years in service.

### 6.4.1 Knowledge and skill (competence) attainment and retention

Several studies worldwide have shown that neonatal resuscitation knowledge and skills decline with time post-training, with skills showing a faster rate of deterioration, compared to knowledge.[111-113,115] Therefore, HBB training alone does not guarantee skill retention several months post-training. In our study we found that video debriefing increased both knowledge and skill attainment and retention. Few studies couple standard HBB training and video debriefing making it difficult to make meaningful comparisons with other studies.

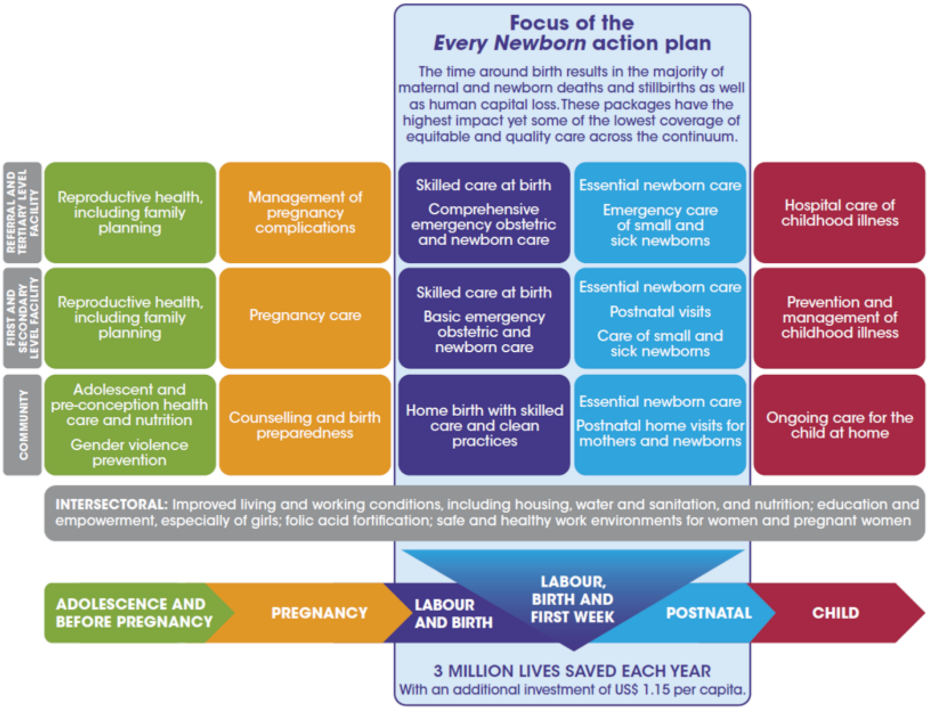
Alternative explanations for the knowledge and skill retention seen in our study include frequent assessments at close intervals that may have pressured the health workers into revising prior to each assessment. A study in Honduras showed that frequent OSCE skills practice among both clinic and hospital-based staff, improved skill retention after six months, post-training.[188,189] In the same study, it was also observed that skills declined at one-month post-training. Similarly, we found a decline in the overall knowledge and skills scores at one-month post-training, with the intervention arm maintaining higher scores than the control group, throughout the follow-up period. Our findings may also add to the list of intervention combinations, to improve learning and skills retention amongst frontline maternal newborn healthcare workers over time. Consequently, this may improve neonatal outcomes, as we aim for the 2030 SDG 3 target of reducing neonatal mortality to less than 12 per 1,000 live births, by that year.

### 6.4.2 Other factors for HBB knowledge and skills retention

Senior SBAs with more than 5 years in service demonstrated inferior knowledge and skills retention. A possible explanation could be that the older or senior SBAs felt that they had the experience, and hence were slow at taking up new changes in newborn care practices. A study by Bang Akash and colleagues (2016), reported low skills retention among senior physicians, who reported being *"too busy to practice neonatal resuscitation skills, despite the provision of equipment in their facilities for daily practice"*.[189] This may, to some extent, explain our findings. We, however, did not conduct a qualitative study to ascertain the reasons for the low knowledge retention among senior SBAs. Lastly, SBAs who conducted routine neonatal resuscitation, also demonstrated less knowledge and skill retention at six months. This might be due to a perceived large workload, and lack of time to read and refresh neonatal resuscitation knowledge and skills.

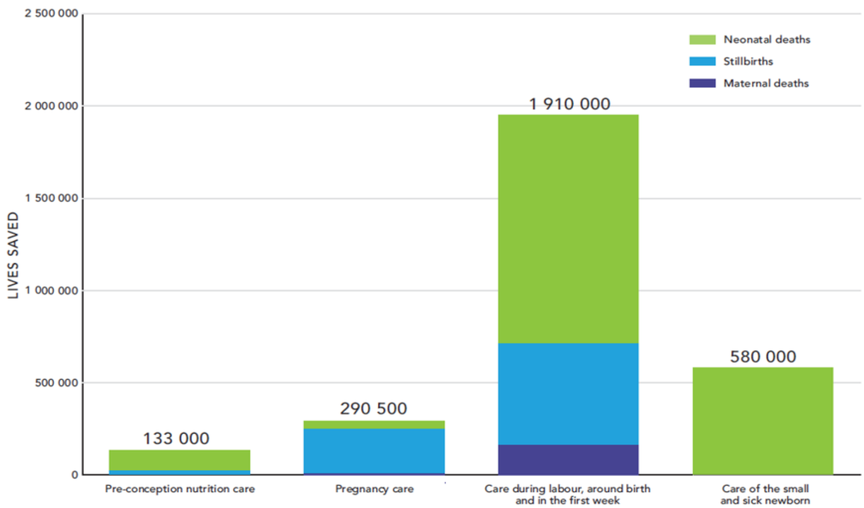
### 6.4.3 Proven life-saving interventions along the continuum of care

In our study, there was low universal coverage for maternal newborn health care to ensure a healthy start in childhood. Following the inability reach the MDG by 2015, the Every Newborn Action Plan (ENAP) was adopted by global countries for the provision of equal high quality care to every newborn.[27] The basis of this was, the observed slow reduction of neonatal mortality of the 15 year period despite evident reduction in under-five and infant mortality. In addition to ENAP, there are other care packages for good birth outcomes along the continuum of care that have been discussed in section 1.6.5 of this thesis, Figure 10.




*Source: The Lancet* Every Newborn Series, Mason E et al. *Lancet*, 2014 (*27*).

Figure 10. Care packages in the continuum of care for every mother and baby




*Source: The Lancet* Every Newborn Series, Bhutta Z et al. *Lancet*, 2014 (*6*).

Figure 11. Lives that could be saved by 2025 by Universal coverage of care packages[190]

In addition to the above care packages, the WHO introduced the labour care aimed at providing individualised care for a positive childbirth experience for every woman. The care guide is an improved partograph except for the introduction of some other elements such as supportive care, maternal and fetal cut-offs for emergency actions and the separate parts for mother and infant care all on the same page.[191] Implementation of these care packages could potentially save thousands of lives in different stages of the human life cycle along the continuum of care, Figure 11.

Lastly, in 2022, WHO added 11 new recommendations for care and support of low birthweight and preterm birth, Box 2.[192]

| Box 2 WHO's 11 new recommendations and good practice statement for care of preterm or low birthweight infants |
| --- |
| 1) Kangaroo mother care (KMC) for preterm or LBW infants should be started as soon as possible after birth<br>2) Probiotics may be considered for human-milk-fed preterm infants <32 weeks gestation<br>3) Application of topical oil to the body of preterm or LBW infants may be considered<br>4) Continuous positive airway pressure (CPAP) therapy may be considered immediately after birth for very preterm infants<br>5) For preterm infants <37 weeks' gestation who need CPAP therapy, bubble CPAP may be considered rather than other pressure sources (e.g., ventilator CPAP)<br>6) Caffeine is recommended for the treatment of apnoea in preterm infants <37 weeks' gestation<br>7) Caffeine is recommended for extubation and may be considered for the prevention of apnoea in in preterm infants <37 weeks' gestation<br>8) Family involvement in the routine care of preterm or LBW infants in health-care facilities is recommended<br>9) Families of preterm or LBW infants should be given extra support to care for their infants, starting in health-care facilities from birth and continued during follow-up post-discharge. The support may include education, counselling, and discharge preparation from health workers, and peer support<br>10) Home visits by trained health workers are recommended to support families to care for their preterm or LBW infant<br>11) Parental leave and entitlements should address the special needs of mothers, fathers, and other primary caregivers of preterm or LBW infants |

## 6.5 Methodological issues

In this section, we summarize the key methodological challenges, discuss mitigation strategies and consider their implications.

### 6.5.1 Methodological issues associated with observational studies

In settings where randomized trials are limited or impossible, observational studies are useful in providing evidence that informs decision-making. This thesis employed two types of observational study designs: the cohort (Papers I – III), and cross-sectional (Paper III) designs.

In the cohort study, the exposed and unexposed groups of pregnant mothers were identified and followed-up for outcomes of small newborns (PB & LBW) at birth (Paper I). In Paper II, the cohort of mother-infant dyads with small newborns (exposed) and those without (unexposed), were subsequently followed-up from birth to 28 days of postnatal life for neonatal death and/or hospitalisation (outcomes). In the cross-sectional study of prevalence of neonatal hypoglycaemia, we identified infants with neonatal hypoglycaemia (outcome), and studied their associations with small newborn (exposure) at the same time. Subsequently, we also prospectively followed this same cohort for the same neonatal adverse outcomes, as for small newborn in Paper II.

Generally, the epidemiological study methods employed in this thesis are prone to several limitations, that affect the exposure-outcome relationships.[193] These limitations are summarized below.

#### *Paper I and II*

Limitations in our findings included but are not limited to:

- Selection bias (selective inclusion and loss to follow-up)
- Misclassification/information bias
- Confounding
- Random error

### 6.5.2 Selection bias

Bias is a systematic error in study design, conduct, or analysis that results in an incorrect estimate of an exposure's effects on the risk of disease.[193] A selection bias is a participant selection method that results in a distorted exposure-outcome relationship, which is not indicative of the true association in the population.

In Paper I, we assessed the incidence of LBW and PB in newborns. LBW and/or PB may happen any time after 28 weeks of gestation. In the randomised trial in which our observational study was nested, inclusions were allowed at any time from 28 or more weeks of gestation. It means that a pregnant woman could be included at, for instance, at 35 weeks of gestation. This also means that not all pregnant women in the study area were followed up from exactly 28 weeks of gestation. Women who had LBW and PB before recruitment into the trial were systematically excluded from our study. This likely caused us to underestimate the true incidence of LBW and PB. This could explain the low incidence of LBW and PB reported in this study.

Furthermore, additional selection biases could have occurred due to loss to follow up resulting from missing birthweight and/or gestational age assessment (GA) of the infants. For the PB, we restricted the analysis to the sample of infants with both GA and birthweight. Approximately 554 infants (30%) of the 1833 in the cohort did not have both birthweight and gestational age measurements and were excluded from the analysis. This could have possibly resulted in a selection bias. That said, in a sensitivity analysis, we found no major differences in socio-demographic characteristics of included and excluded participants. Future studies to estimate the incidence of LBW and PB should aim at enrolling mothers in the first trimester and following up the entire cohort for the remainder of the pregnancy. This would permit more accurate gestational age estimations and provide a more complete cohort.

In Paper III, our estimate of neonatal hypoglycaemia had some limitations that probably resulted in selection bias. First, our inability to follow-up and reach some neonates within their first week of life for NBS, might have resulted in a selection bias. Secondly, since we only examined neonates in their homes, we missed 18/43

(41.9%) hospitalized neonates and we were also unable to reach another 400/1790 non-hospitalized (22.3%) infants within 7 days of postnatal life. Some of these missed infants could have had hypoglycaemia.

### 6.5.3 Misclassification / information bias

This is a systematic error in measurements, and it occurs when information is collected differently between groups, leading to errors in conclusions of possible associations. This may be due to differential (different) or non-differential (no difference) misclassifications between groups.[193]

In Paper III we only performed a single blood glucose measurement, instead of serial blood glucose levels for the assessment of neonatal hypoglycaemia as recommended by the Paediatric Endocrine Society. This was because of resource limitations for serial blood glucose measurements, but also to avoid multiple heal pricks to seemingly healthy infants (an ethical dilemma). This could have resulted in a misclassification of the hypoglycaemic infants. The blood glucose measurements were also done at different post-natal ages, some after several days, when hypoglycaemia was less likely to occur and this could have resulted in underestimation of neonatal hypoglycaemia.

The lack of a gold standard for gestational age estimates (first trimester fetal ultrasonography) in our study, required us to fall back on the use of the New Ballard scoring (NBS) system, for ascertainment of gestational age. The NBS has a sensitivity of 0.333 and specificity of 0.998 compared to early fetal ultrasound scan in determining gestational age.[194] This low sensitivity could have resulted in the misclassification of some infants. Lastly, we were not able to diagnose intrauterine growth retardation among the LBW and PB infants due to lack of both ultrasound equipment and an experienced obstetrician in the study setting. We were therefore not able to assess foetal growth retardation in our cohort.

### 6.5.4 Confounding

Confounding occurs when the observed measure of association between exposure and outcome differs from the truth, because of the influence of a third variable.[195] The third variable should be associated with both the exposure and outcome, without being in their causal pathways.[195] Commonly recognised confounders include age and sex. In all the Papers I – IV, this was controlled for in the analysis phase by multiple regression modelling.

## 6.6 Changes in Paper I

Paper I was amended and extensively modified following the examination committee's comments. Unfortunately, by the time the comments were returned to the candidate, Paper I was already published in its previous form, see appendix. In view of the comments from the committee, there are a number of changes that should preferably have been made before its publication and these have been made in the amended manuscript of Paper I. The main changes are:

- the overlap between preterm birth (PB) and low birthweight i.e., intrauterine growth restriction, have been included in the introduction
- data on the proportion of low birthweight infants who were born preterm and vice versa were added
- to try to gauge the error margin on the estimate of the proportion of preterm births in this cohort, we included the proportion of mothers recruited no later than at 28 weeks of gestation and noted that more than 80% were recruited at 28 weeks while a good number of mothers did not know their gestational age by LMP. In order not to leave out preterm births occurring among the latter group of mothers, we estimated PB among all the included mother-infant dyads with both birthweight and gestational age estimation by the new Ballard scoring system (NBS).

## 6.7 Strengths of the studies in this thesis

There were several strengths in our study. Firstly, we used a community-based cohort – likely to reflect the community at large. Secondly, we were able to follow-up and obtain birthweight within 48 hours on 1556/1833 (85%) of the cohort, minimising the risk of selection bias, in settings where more than 40% of deliveries happen at home, obtaining birthweight for 85% of the cohort was commendable. The mothers were interviewed shortly after the delivery, minimising the likelihood of recall bias. Thirdly, in Paper I and II, we used hard, explicitly defined outcome measures (LBW, PB, neonatal death, and hospitalisation). This reduced the likelihood of misclassification/information bias.

Paper IV was a cluster randomized trial. On average, when successful, randomization makes study groups comparable by balancing potential confounders between the study arms. To a great extent, we achieved balance in this study.

# 7. Conclusions and recommendations

## 7.1 Conclusions

Albeit the limitations of the study, the findings reported in this thesis are still relevant to guide interventions to reduce burden of small newborns and its adverse outcomes – neonatal deaths, hypoglycaemia and asphyxia. Therefore, we conclude as follows:

### 7.1.1 Burden and outcomes of LBW and PBs in post-conflict Northern Uganda

- The incidence of LBW in our study was 7.4% and PB was 5.0%.
- Intermittent preventive treatment for malaria was associated with a reduced risk of LBW by 40% while HIV infection was associated with a three times increased risk of both LBW and PB.
- Maternal formal education for ≥7 years was associated with an 80% reduced risk of LBW and PB.
- A total of 103 LBW and 91 PB infants per 1000 live births died in the neonatal period – higher than the national rates. Neonatal death in post-conflict northern Uganda was associated with both low birthweight and preterm birth, and birth asphyxia.

### 7.1.2 The prevalence and outcomes of neonatal hypoglycaemia

- The proportion of neonatal hypoglycaemia was 2.5%.
- Factors associated with an increased risk of hypoglycaemia included preterm birth, delayed breastfeeding initiation, and early blood glucose measurement (before 3 days of age).
- Infants with neonatal hypoglycaemia had an increased risk of neonatal hospitalisation and severe outcomes.

### 7.1.3 Video debriefing for improved competence of frontline SBAs

Adding video debriefing to HBB training improved the overall skills and competence (combined knowledge and skills) attainment in the immediate (2 days) post-training period and, knowledge retention over six-month follow-up period.

## 7.2 Recommendations

### 7.2.1 Low birthweight and preterm burden and outcomes

Given the high risk of morbidity and mortality among LBW and PBs, we recommend the following:

- Urgent need to improve the coverage and quality of emergency obstetric care of pregnant mothers such as foetal heart monitoring, corticosteroids for preterm labour and skilled birth attendance.
- Studies to identify the effectiveness of proven lifesaving integrated intervention combinations like aspirin, antenatal corticosteroids, peer counselling, early breastfeeding initiation, IPT are required. These may further reduce
    - The frequency of LBW and PBs.
    - The frequency of adverse events (severe outcomes).
- Targeted routine neonatal hypoglycaemia screening for high-risk infants (LBW and PB) may be considered. There is a need to emphasise promotion of community- and health facility-based early initiation of and frequent breastfeeding practices to reduce neonatal hypoglycaemia and its related complications.

### 7.2.2 Video debriefing for improved competence among SBAs

- We recommend additional research with cost-effectiveness analysis to support the addition of video debriefing to the current standard HBB training curricula. Further research into the facility-based neonatal mortality in the short- and long-term may also be considered.

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# I

# Incidence and risk factors for low birthweight and preterm birth in post-conflict Northern Uganda: a community-based cohort study


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## Abstract

### Background

Annually, an estimated 20 million (13%) low birthweight (LBW) and 15 million (11.1%) preterm infants are born worldwide. The paucity of data and reliance on hospital-based studies from low-income countries make it difficult to quantify the true burden of LBW and PB, the leading cause of neonatal and under-five mortality. We aimed to determine the incidence and risk factors for LBW and preterm birth in Lira district of Northern Uganda.

### Methods

This was a community-based cohort study, nested within a cluster-randomized trial, designed to study the effect of a combined intervention on facility-based births. In total, 1877 pregnant women were recruited into the trial and followed from ≥28 weeks of gestation until birth. Infants of 1556 of these women had their birthweight recorded and 1279 infants were assessed for preterm birth using a maturity rating, the New Ballard Scoring system. Low birthweight was defined as birthweight <2.5kg and preterm birth was defined as birth before 37 completed weeks of gestation. The risk factors for low birthweight and preterm birth were analysed using a multivariable generalized estimation equation for the Poisson family.

### Results

The incidence of LBW was 121/1556 or 7.3% (95% Confidence interval (CI): 5.4% – 9.6%). The incidence of preterm births was 53/1279 or 5.0% (95% CI: 3.2% – 7.7%). Risk factors for LBW were maternal age ≥35 years (adjusted Risk Ratio or aRR: 1.9, 95% CI: 1.1–3.4), history of a small newborn (aRR: 2.1, 95% CI: 1.2 – 3.7), and maternal malaria in pregnancy (aRR: 1.7, 95% CI: 1.01 – 2.9). Intermittent preventive treatment (IPT) for malaria, on the other hand, was associated with a reduced risk of LBW (aRR: 0.6, 95% CI: 0.4 – 0.8). Risk factors for preterm birth were maternal HIV infection (aRR: 2.9, 95% CI: 1.1 – 7.3) while maternal education for ≥7 years was associated with a reduced risk of preterm birth (aRR: 0.2, 95% CI: 0.1 – 0.98) in post-conflict northern Uganda.

### Conclusion

The incidence of LBW and PB were low, compared to the national, sub-Saharan Africa and global estimates – possibly due to methodological limitations. Advanced maternal age ≥ 35 years and history of a small newborn were associated with increased risk of low birthweight. Maternal formal education for ≥7 years was associated with a reduced risk of LBW and PB while HIV infection was associated with an increased risk of PB.



**Key words:** Preterm birth, low birthweight, risk factors, community-based, cohort study.

## Introduction

Of the 140 million infants born worldwide in 2014, an estimated 20 million (13%) low birthweight (<2.5 kg).[1] Ninety percent (18/20 million) of LBW infants were born in low- and middle-income countries (LMICs).[2] In sub-Saharan Africa, LBW prevalence varied from 7.0% to 18.0%, with the highest prevalence observed in malaria-based studies in Tanzania.[2] According to the Uganda Bureau of Statistics (UBOS) 2011, 10.4% of all live-born infants nationwide and 11.4% in the northern part of the country are LBW.[3] Low birthweight may be a result of foetal growth restriction (also called intrauterine growth restriction, IUGR), preterm birth (birth before 37 weeks of gestation) or a combination of these. About 41% of LBW infants are estimated to be preterm.[4] IUGR is foetal weight <10 centile of the normal weight for gestational age while SGA is weight <10$^{th}$ centile at birth.[5] Assessment of foetal growth requires antenatal ultrasound scanning which may be scarce or unavailable in low-resource settings.

In 2010, an estimated 15 (uncertainty range 12–18) million preterm infants were born worldwide.[6] The global PB estimates ranges from 5% in Europe to 18% in some sub-Saharan African countries.[6] Sub-Saharan Africa and South Asia contribute 52% - 60% of the global PB burden.[6] In Uganda, reports of the proportion of PBs range from 4.1% to 15%.[6,7] In communities of post-conflict northern Uganda, however, its true burden is unknown.

Multiple maternal and fetal causes of LBW and/or PB (small birth size) have been described.[8] The age of the mother, either young (teenage 12-16 years) or old (≥35 years) has been linked to increased risk of small birth size.[9,10] Low maternal socio-economic and education status has been associated with small birth size.[11-14] Furthermore, maternal ill-health during pregnancy such as malaria and HIV infection, low body mass index (BMI) or low gestational weight gain, and hypertension have also been associated with small birth size.[15,16] A history of having given birth previously to a small infant has also been associated with LBW and/or PB recurrence in subsequent pregnancies.[16,17] Whereas some studies report increased risk of small birth size among women who do excessive physical work, a 2013 meta-analysis found little to no effect of the same on small birth sizes.[18] Foetal factors associated with LBW and PB include: congenital malformations, multiple foetuses, and genetic factors.[19,20]

In high-income countries, common causes of small birth size include provider-initiated caesarean section and assisted reproduction,[8] while in low-resource settings, it is related to maternal infections, low socio-economic status, malnutrition, and history of preterm birth or low birthweight.[8] In post-conflict northern Uganda, however, the social disruption, lack of schooling and displacement caused by the 20 years of conflict may have modified the burden and some of the known risk factors for small birth size. Few studies exist to describe the burden of LBW and PB during the post-conflict period in northern Uganda.[3] We hypothesise that 1) the incidence of LBW and PB in northern Uganda is higher than the global estimates 2) advanced maternal age >=35 years is associated with an increased risk of LBW and PB than maternal age 20-34 years.

To achieve the SDG 3.2 target of neonatal mortality below 12 per 1000 live births by 2030, there is a need to generate post-conflict context specific data on the small newborns' (LBW and PB) health burden and associated modifiable risk factors. We, therefore, aimed to 1) estimate the incidence of and 2) determine risk factors for low birthweight and preterm birth in post-conflict northern Uganda.

## Methods

This was a cohort study nested within the Survival Pluss cluster randomized trial. The Survival Pluss study assessed the effect of an integrated package consisting of peer support by pregnancy buddies, provision of mama kits at household level (as opposed to health facility distribution) and mobile phone messaging on facility-based births. In the trial, pregnant women were enrolled at ≥ 28 weeks of gestation and followed up to delivery (ClinicalTrials.gov number NCT0260505369).

The study was conducted in Lira District, Northern Uganda from January 2018 to February 2019. Lira District had a population of about 400,000 people in 2010, dwelling in 13 sub-counties, a city and 751 villages. Lira district was chosen based on its being a post-conflict area with poor maternal and child health indicators, low proportion of health facility deliveries, high neonatal mortality, and limited data on LBW and PBs burden and associated risk factors.[21] The study sites were Aromo, Agweng, and Ogur sub-counties; also chosen because they had the poorest maternal and child health indicators.[9] Each sub county had at least one public health centre (HC), either level II (only outpatients), level III (having a maternity and in-patients) and level IV (having a surgical theatre). Furthermore, each sub-county had one health centre with maternity (health centre, HC III or HC IV), or two additional lower-level health centres without maternity (HC II). Two of the HC IIIs (Agweng and Aromo), however, were not conducting deliveries before the project inception.

A total of 1877 mothers were recruited into the trial at $\geq$28 weeks of gestation and followed up to birth. Of these, 1556 mother-infant dyads had birthweight (sample used for LBW incidence and risk factors). Of the 1556 mothers, 1279 had both a gestational age estimate using the New Ballard Score (NBS) and birthweight (sample analysed for PB incidence and risk factors).

Birthweight was recorded either at the health facility or by one of the 46 research assistants within 2 days of birth. The NBS for gestational age assessment had to be done within 7 days of birth and was conducted by 4 specially trained midwives and nurses. This explains why not all babies had gestational age estimates.

The primary outcomes were incidence of 1) low birthweight births and 2) preterm births. Independent or exposure variables were maternal and infant factors. Maternal *socio-demographic* (maternal age in completed years, years of education, paternal occupation, marital status, wealth index groups, intervention, and domestic water source) and *clinical factors (*parity, HIV, malaria in pregnancy, intermittent preventive treatment (IPT) for malaria in pregnancy, small newborn history, multiple pregnancy, and antenatal care (ANC) attendance and *infant factor (*sex) were analysed for association with LBW and PB. Other risk factors for small newborns such as maternal hypertension, diabetes mellitus, and body mass index (BMI) were not part of the data collection and is therefore not assessed.

A low birthweight (LBW) was defined as birthweight < 2.5kg at birth while preterm birth (PB) was defined as being born after 28 weeks of gestation but before 37 completed weeks of gestation.[1] We calculated the incidence (risk) as the number events (LBW or PB) divided by total number of live births (population at risk), during the study period from January 2018 to February 2019, expressed as a percentage. Birthweight was measured using a digital floor scale with mother/child function (seca, Hamburg, Germany) and recorded to the nearest 2 decimal points in kilograms. Gestational age (GA) was estimated using the New Ballard Score (NBS), which employs both physical and neuromuscular maturation. The total physical maturation (PM) and neuromuscular maturation (NM), also known as maturity rating total scores (MRTS), was correlated with gestational age, recorded in completed weeks. The MRTS, ranging from –10 to 50, were then extrapolated to fetal age in weeks (20 to 44). Maternal age was recorded in completed years and categorised into three groups as 12–19, 20–34, and 35–49 years. Education was recorded in years of completed schooling and dichotomized as 0–6 and 7 or more years in school. Marital status was categorised as binary variable into 'married' or 'single/separated/divorced/widowed'. Wealth index quintiles were calculated using Gini index based on several key household assets and classified ranging from the 1 'poorest' to 5 'wealthiest' quintiles. This was further sub-grouped into three wealth groups as follows: the lower 40% (1$^{st}$ – 2$^{nd}$ quintiles), the middle 40% (3$^{rd}$ – 4$^{th}$ quintiles) and the upper 20% (5$^{th}$ quintile). Paternal occupation was categorized during analysis as farmer, employed or unemployed. Domestic water source was categorised as 'tap/borehole' or 'spring/well/river/ponds. History of a small newborn was recorded as 'yes' if the mother had history of a small baby by her own assessment in prior pregnancy. Parity was the number of pregnancies the mother had before, and further re-categorised as 'prime gravida (first time mother)', '1–6' and '7 or more' children. The presence of maternal illnesses during pregnancy such as malaria or HIV were recorded as ('yes' 'no', or 'unknown') based on antenatal test results. Antenatal care (ANC) attendance was recorded as 'yes' if the woman attended antenatal clinic at least once during the current pregnancy. Maternal malaria IPT in pregnancy was recorded as 'yes' if the mother received intermittent preventive treatment for malaria during pregnancy.

Intervention was recorded as 'yes' if the mother received the Survival Pluss intervention package (Mamakit, SMS, and peer buddies) during pregnancy.

We analysed sub-samples of mother-infant pairs from the Survival Pluss cohort who had infants with birthweight (1556) or both birthweight and gestational age by NBS assessment (1279), respectively. We compared the included to the excluded sample and there was minimal difference in baseline characteristics between the analysed and excluded groups, (Table 1). The Survival Pluss study included and followed all pregnant women in the participating communities from 28 weeks of gestation, who had no intention of moving away from the study area within a year of enrolment and who had no psychiatric illness that could inhibit the informed consent process. We excluded infants whose parents declined newborn examinations, those who died at birth or who had severe congenital abnormalities (anencephaly and exomphalos) and those without birthweight (for LBW) and without NBS (for PBs).

**Study procedures**

In each cluster, pregnant women were identified by a community recruiter (pregnancy monitor) who was a mature woman living within the cluster, of good repute and selected by community members. A total of 250 pregnancy monitors were trained on how to identify pregnant women in their communities and inform the trial team. They were each given a mobile phone to enable them to communicate with the trial team. Whenever a pregnant woman was identified by the community recruiter informed the research assistant and together organised and visited the pregnant woman at home.

Prior to recruitment, 50 research assistants (RAs) were trained on the study protocol, weight measurement, and electronic data collection tool, and the open data kit (ODK) software (https://opendatakit.org/). Four (04) of 50 RAs were further trained on the New Ballad Scoring system for gestational age assessment. All the RAs except the nurses and midwives, had qualifications of at least senior four certificate, could read and comprehend the English and the local Lango language, and were able to use smartphones. The RAs who administered the NBS were in addition trained skilled birth attendants, nurses and midwives. Pregnant mothers were identified by community recruiters who informed the study team. The research assistants were then dispatched to see and interview the identified pregnant mothers in their homes. Those who met the inclusion criteria were consented and recruited. The recruitment questionnaires were administered to the mothers and the information was entered using ODK installed on a mobile phone. Maternal socio-demographic, and gynaecological histories were collected. Those mothers receiving integrated intervention packages of mobile phone messages, mama kit, and peer counselling were then given the package, while those in the control arm were allowed to continue with their routine antenatal care. All the enrolled pregnant women were followed up to birth and postnatally to two and seven days, for birthweight and administration of the NBS respectively. The neonatal anthropometrics (birthweight) measurements and the NBS were done within two days and seven days for accurate determination of birthweight and gestation age, respectively. At the onset of labour, birth or after delivery, the same community recruiters informed the study team who in turn visited the mother-infant dyads at birth for delivery questionnaire administration and anthropometric (birthweight, length, head, chest and abdominal circumferences) measurements. The weighing scales were calibrated while the measuring tapes, and length/height boards were checked for accuracy before each field visit and before each measurement was taken. The weighing scales were checked for accuracy daily with known standard weights. Data was collected using standardized pre–coded questionnaires in ODK, and immediately sent to the server for safe custody by the data manager. Data cleaning and checking for completeness were done for quality control throughout the data collection process.

A total of four research nurses and midwives were trained on the NBS tool. The overall intra-rater (percentage agreement: 82.56%, kappa: 0.806, 95% CI: 0.788 – 0.823) and inter-rater (percentage agreement: 77.5%; kappa: 0.774, 95% CI: 0.613 – 0.936) reliability for the Ballard scoring tool were strong. The principal investigator (BO) worked with and supervised the research assistants on data collection and documentation.

**Statistical analysis**

The data collected using ODK was sent to a server from where it was downloaded to Stata 14 (Stata Corp, College Station, Texas, US) for analysis. The incidence of LBW and PB were sex standardized and cluster adjusted and presented as the proportion of LBW and PBs to the total number of live births reported in percent. Descriptive statistics for categorical variables were summarized into proportions and the results presented in Tables (2 and 3). Inferential statistics (the risk factors for LBW and PB), were analysed using bivariable and multivariable generalised estimation equation for the binary categorical outcome of LBW and PB (Tables 2 and 3). Significant factors with p value $\leq 0.05$ at bivariable analysis were taken into the multivariable generalized estimation equation model with a log link to Poisson family, adjusting for clustering and potential confounding. Known risk factors for LBW and PB such as infant sex, wealth index, and integrated intervention were also added into the final model. The crude and adjusted risk ratios were compared during the multivariable regression analysis. A difference of $\geq$10% between crude and adjusted risk ratios were considered confounding.

### Ethical considerations

Ethical clearance was obtained from Makerere University School of Medicine Research and Ethics Committee (SOMREC no. 2015/085), the Uganda National Council for Science and Technology (UNCST no. HS 2478) and REK Vest in Norway (No. 2018/58/REK Vest). Permission was obtained from the district and health facility administrations. The study was also registered with ClinicalTrial.gov NCT02605369). Written informed consents were obtained from all Survival Pluss study participants. Participant confidentiality was maintained through the use of password protected mobile phones and computers.

## Results

### Study profile

Of the 1877 pregnant women recruited into Survival Pluss trial, 1480 (78.9%) were recruited at 28 weeks of gestational age by last menstrual period. A total of 44 were lost to follow-up, 277 had missing birthweight and further 277 were not reached in time for gestational age estimation by NBS. Of those with birthweight, 7.8% (121/1556) were LBW and of those with gestational age estimate, 4.1% (53/1279) were assessed to be born preterm. A total of 20 (19.0%) of the LBW infants with gestational age were considered preterm, while 20 (37.7%) of preterm infants were low birthweight (Figure 1).

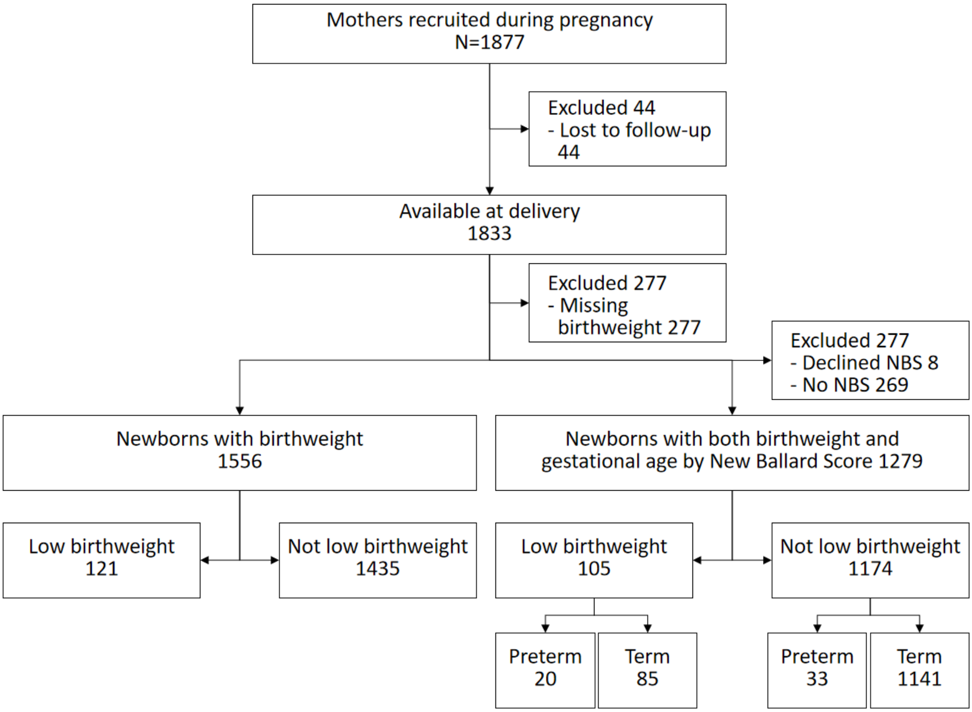


**Figure 1. Study profile.**

## Baseline and clinical characteristics of study participants

Of the 1556 mother-infant dyads, 1305 (84.0%) were recruited at 28 weeks of gestational age by LMP), a quarter of the mothers were first time mothers (prime gravida), 22 (1.4%) had twins, and 90% were married. Most of the fathers were subsistence farmers. Most families used tap or borehole water for domestic consumption. Around 5% of the mothers stated they had HIV, while up to 2% did not know their HIV status. Close to 14% of mothers had prior history of a small newborn in the most recent (second last) delivery. The male to female ratio approximated 1:1, Table 1. Similarly, of the 1279 infants with birthweight, gestational age by NBS and

Table 1. Comparison of baseline characteristics between included and excluded study participants in the two analyses – low birthweight and preterm birth – in Northern Uganda.

| | Low birthweight | | | | Preterm birth | | | |
|---|---|---|---|---|---|---|---|---|
| | All N=1877 n (%) | Analysed N=1556 n (%) | Excluded N=321 n (%) | p value | All N=1877 n (%) | Analysed N=1279 n (%) | Excluded N=598 n (%) | p value |
| **Maternal characteristics** | | | | | | | | |
| *Maternal age* | | | | | | | | |
| 12-19 years | 510 (27.2) | 415 (26.7) | 95 (29.6) | | 510 (27.2) | 330 (25.8) | 180 (30.1) | |
| 20-34 years | 1174 (62.5) | 982 (63.1) | 192 (59.8) | 0.325 | 1174 (62.5) | 815 (63.7) | 359 (60.0) | 0.017 |
| >=35 years | 193 (10.3) | 159 (10.2) | 35 (10.6) | | 193 (10.3) | 134 (10.5) | 59 ( 9.9) | |
| *Maternal education* | | | | | | | | |
| 0-6 years | 1515 (80.7) | 1246 (80.1) | 269 (83.8) | | 1515 (80.7) | 1032 (80.7) | 483 (80.8) | |
| >=7 years | 362 (19.3) | 310 (19.9) | 52 (16.2) | 0.117 | 362 (19.3) | 247 (19.3) | 115 (19.2) | 0.896 |
| *Maternal vocational education* | | | | | | | | |
| No | 1663 (88.6) | 1371 (88.1) | 292 (92.0) | | 1663 (88.6) | 1131 (88.4) | 532 (89.0) | |
| Yes | 214 (11.4) | 185 (11.9) | 29 ( 8.9) | 0.224 | 214 (11.4) | 148 (11.6) | 66 (11.0) | 0.700 |
| *Marital status* | | | | | | | | |
| Married | 1708 (91.0) | 1417 (91.1) | 291 (90.7) | 0.495 | 1708 (91.0) | 1166 (91.2) | 542 (90.6) | 0.557 |
| Single/separated/divorced/widow | 169 ( 9.0) | 139 ( 8.9) | 30 ( 9.3) | | 169 ( 9.0) | 113 (8.8) | 56 ( 9.4) | |
| *Wealth index* | | | | | | | | |
| Lower 40% | 837 (44.6) | 708 (45.5) | 129 (40.2) | | 837 (44.6) | 574 (44.9) | 263 (44.0) | |
| Middle 40% | 665 (35.4) | 547 (35.2) | 118 (36.8) | 0.329 | 665 (35.4) | 465 (36.4) | 200 (33.4) | 0.139 |
| Upper 20% | 375 (20.0) | 301 (19.3) | 74 (23.0) | | 375 (20.0) | 240 (18.8) | 135 (22.6) | |
| *Father's occupation* | | | | | | | | |
| Farmer | 1275 (67.9) | 1058 (68.0) | 217 (67.6) | | 1275 (67.9) | 883 (69.1) | 392 (65.5) | |
| Employed | 390 (20.8) | 348 (22.4) | 42 (13.1) | 0.022 | 390 (20.8) | 274 (21.4) | 116 (19.4) | 0.688 |
| Unemployed | 168 ( 9.0) | 150 ( 9.6) | 18 ( 5.6) | | 168 ( 9.0) | 122 ( 9.5) | 46 ( 7.7) | |
| Missing | 44 ( 2.3) | 0 ( 0.0) | 44 (13.7) | | 44 ( 2.3) | 0 ( 0.0) | 44 ( 7.4) | |
| *Domestic water source* | | | | | | | | |
| Tap/Borehole | 1188 (63.3) | 977 (62.8) | 211 (65.7) | 0.459 | 1188 (63.3) | 802 (62.7) | 386 (64.6) | 0.268 |
| Spring/river/well/stream/pond | 689 (36.7) | 579 (37.2) | 110 (34.3) | | 689 (36.7) | 477 (37.3) | 212 (35.4) | |
| *Intervention* | | | | | | | | |
| No | 855 (47.2) | 740 (47.6) | 145 (45.2) | | 885 (47.2) | 601 (47.0) | 284 (47.5) | |
| Yes | 992 (52.9) | 816 (52.4) | 176 (54.8) | 0.625 | 992 (52.8) | 678 (53.0) | 314 (52.5) | 0.956 |
| *Facility Delivery* | | | | | | | | |
| No | 644 (34.3) | 484(31.1) | 160 (49.8) | | 644 (34.3) | 397 (31.0) | 247 (41.3) | |
| Yes | 1233 (65.7) | 1072(68.9) | 161 (50.2) | 0.000 | 1233 (65.7) | 882 (67.0) | 351 (58.7) | 0.000 |
| **Maternal clinical characteristics** | | | | | | | | |
| *History of small infant* | | | | | | | | |
| No | 1131 (60.2) | 985 (63.3) | 146 (45.5) | | 1131 (60.3) | 964 (75.4) | 167 (30.2) | |
| Yes | 317 (16.9) | 218 (14.0) | 99 (30.8) | 0.000 | 317 (16.9) | 40 ( 3.1) | 277 (50.0) | 0.000 |
| *Prime gravida* | *429 (22.9)* | *353 (22.7)* | *76 (23.7)* | | *429 (22.9)* | *275 (21.5)* | *154 (27.8)* | |
| *Parity* | | | | | | | | |
| Prime gravida | 429 (22.9) | 353 (22.7) | 76 (23.7) | | 429 (22.9) | 275 (21.5) | 154 (25.7) | |
| 1-6 | 1257 (67.0) | 1043 (67.0) | 214 (66.8) | 0.857 | 1257 (67.0) | 872 (68.2) | 385 (64.4) | 0.025 |
| 7 or more | 191 (10.2) | 160 (10.3) | 31 ( 9.7) | | 191 (10.2) | 132 (10.3) | 59 ( 9.9) | |
| *Maternal HIV infection* | | | | | | | | |
| No | 1708 (91.0) | 1455 (93.5) | 253 (78.8) | | 1708 (91.0) | 1205 (94.2) | 503 (84.1) | |
| Yes | 83 ( 4.4) | 73 ( 4.7) | 10 ( 3.1) | 0.000 | 83 ( 4.4) | 61 ( 4.8) | 22 ( 6.7) | 0.000 |
| Unknown | 86 ( 4.6) | 28 ( 1.8) | 58 (18.1) | | 86 ( 4.6) | 13 ( 1.0) | 73 (12.2) | |
| *Antenatal attendance* | | | | | | | | |
| No | 395 (21.0) | 352 (22.6) | 43 (13.4) | | 395 (21.0) | 283 (22.1) | 112 (18.7) | |
| Yes | 1482 (79.0) | 1204 (77.4) | 278 (86.6) | 0.000 | 1482 (79.0) | 996 (77.9) | 486 (81.3) | 0.088 |
| *IPT[a] for malaria in pregnancy* | | | | | | | | |
| No | 764 (40.7) | 704 (45.2) | 60(18.7) | | 764 (40.7) | 695 (54.3) | 69 (11.5) | |
| Yes | 1113 (59.3) | 852 (54.8) | 261 (81.3) | 0.000 | 1113 (59.3) | 584 (45.7) | 529 (88.5) | 0.000 |
| *Maternal malaria in pregnancy* | | | | | | | | |
| No | 602 (32.1) | 502 (32.3) | 100 (31.2) | | 602 (32.1) | 272 (45.5) | 330 (25.8) | |
| Yes | 459 (24.4) | 388 (24.9) | 71 (22.1) | 0.245 | 459 (24.4) | 117 (19.6) | 342 (26.7) | 0.000 |
| Unknown | 816 (43.5) | 666 (42.8) | 150 (46.7) | | 816 (43.5) | 209 (35.0) | 607 (47.5) | |
| **Infant sex** | | | | | | | | |
| Female | 892 (47.5) | 757 (48.7) | 135 (42.0) | | 892 (47.5) | 620 (48.5) | 272 (45.5) | |
| Male | 943 (50.2) | 799 (51.3) | 144 (44.9) | 0.950 | 943 (50.2) | 659 (51.5) | 284 (47.5) | 0.816 |
| Missing | 42 ( 2.3) | 0 ( 0.0) | 42 (13.1) | | 42 ( 2.2) | 0 ( 0.0) | 42 ( 7.0) | |

N/n (%) frequency (percentage), [a] IPT = Intermittent preventive treatment for malaria random blood glucose, 1088/1279 (85.1%) were recruited at 28 weeks of gestation by LMP, while 30(2.8%) were unsure of their LMP. Due to the low literacy rates and the unreliability of gestational age (GA) estimation by LMP, we decided to analyse the entire sample of mothers with infant birthweight and GA for the PB estimates. An estimated 19.0% (20/105) LBW infants were preterm and 37.7% (20/53) preterm infants were low birthweight.

**The incidence of low birthweight and preterm birth**

*Low birthweight*

The number of low birthweight infants was 121/1556, 7.7%. The sex and cluster adjusted incidence of LBW in post-conflict northern Uganda was 7.3% (95% Confidence interval (CI): 5.4% – 9.6%).

*Preterm birth*

The incidence of preterm births assessed by NBS was 53/1279 or 4.1%. The sex and cluster adjusted incidence of PB in post-conflict northern Uganda was 5.0% (95% CI: 3.2% – 7.7%). The New Ballard Score being subjective, we analysed in a sensitivity analysis, the effect of potential systematic over-scoring of the maturity rating total score on the incidence of preterm birth (Table 2). The crude and the sex and cluster adjusted incidence of preterm birth is presented in case the infants were over-scored by 1, 2, 3, or 4 maturity rating total scores (MRTS).

**Table 2. Sensitivity analysis of the incidence of preterm birth based on the New Ballard scores among 1279 infants in Northern Uganda.**

| | Crude incidence of preterm birth (95% CI) | | Cluster and sex adjusted incidence of preterm birth (95% CI) | |
|---|---|---|---|---|
| Using the original New Ballard Score | *4.1%* | *(3.0% - 5.8%)* | *5.0%* | *(3.2% - 7.7%)* |
| Subtracting 1 score point from the New Ballard Score | 5.5% | (4.4% - 6.9%) | 6.4% | (4.4% - 9.2%) |
| Subtracting 2 score points from the New Ballard Score | 7.8% | (6.5% - 9.6%) | 8.6% | (6.1% - 12.2%) |
| Subtracting 3 score points from the New Ballard Score | 12.1% | (10.4% - 14.0%) | 13.1% | (10.0% - 16.9%) |
| Subtracting 4 score points from the New Ballard Score | 17.1% | (15.2% - 19.3%) | 17.8% | (14.6% - 21.4%) |

CI confidence interval

Further analysis of the data set excluding mothers recruited at 37 or more weeks of gestation by last menstrual period, yielded an incidence proportion of 4.0% (95% CI: 3.0 – 5.4) of the 1,234 infants with PB, a similar result as the cohort finding above.

*Small newborns*

A total of 138 of 1279 (10.8%, 95% CI: 8.9 – 13.0) were small newborns (either LBW and/ or PB). Another 20/1279 (1.6 %, 95% CI: 1.0 – 2.4) were born both LBW and PB in our cohort.

## Risk factors for low birthweight and preterm birth

*Low birthweight*

The factors that were associated with an increased risk of a low birthweight infant in our cohort were advanced maternal age (≥35 years), history of a small newborn in prior pregnancy, malaria infection, and unknown malaria status in pregnancy, Table 3.

**Table 3. Bivariable and multivariable analysis of risk factors for low birthweight in northern Uganda.**

| Characteristics | All N=1556 n (%) | LBW N=121 n (%) | Crude RR (95% CI) N=1556 | p value | Adjusted RR (95% CI) N=1556 | p value |
|---|---|---|---|---|---|---|
| **Maternal characteristics** | | | | | | |
| *Maternal age* | | | | | | |
| 12-19 years | 415 (26.7) | 40 (33.1) | 1.4 (1.0 – 2.0) | 0.048 | 1.3 (0.8 – 2.1) | 0.351 |
| 20-34 years | 982 (63.1) | 67 (55.4) | Ref | | | |
| ≥35 years | 159 (10.2) | 14 (11.6) | 1.3 (0.9 – 1.9) | 0.183 | **1.9 (1.1 – 3.4)** | *0.021* |
| *Maternal education* | | | | | | |
| 0-6 years | 1246 (80.1) | 91 (75.2) | Ref | | | |
| ≥7 years | 310 (19.9) | 30 (24.8) | 1.3 (0.9 – 2.0) | 0.190 | 1.4 (0.9 – 2.3) | 0.102 |
| *Maternal vocational education* | | | | | | |
| No | 1371 (88.1) | 103 (85.1) | Ref | | | |
| Yes | 185 (11.9) | 18 (14.9) | 1.3 (0.8 – 2.1) | 0.297 | | |
| *Marital status* | | | | | | |
| Married | 1417 (91.1) | 110 (90.9) | 1.0 (0.5 – 1.8) | 0.951 | | |
| Single/separated/divorced/widowed | 139 ( 8.9) | 11 ( 9.1) | Ref | | | |
| *Wealth index groups* | | | | | | |
| Lower 40% | 708 (45.5) | 62 (51.2) | Ref | | | |
| Middle 40% | 547 (35.2) | 40 (33.1) | 0.8 (0.6 – 1.3) | 0.379 | 0.8 (0.6 – 1.3) | 0.402 |
| Upper 20% | 301 (19.3) | 19 (15.7) | 0.7 (0.5 – 1.2) | 0.171 | 0.7 (0.4 – 1.2) | 0.255 |
| *Father's occupation* | | | | | | |
| Farmer | 1058 (68.0) | 87 (71.9) | Ref | | | |
| Employed | 348 (22.4) | 22 (18.2) | 1.0 (0.5 – 1.8) | 0.929 | | |
| Unemployed | 150 ( 9.6) | 12 ( 9.9) | 0.8 (0.5 – 1.2) | 0.237 | | |
| *Domestic water source* | | | | | | |
| Tap/Borehole | 977 (62.8) | 72 (59.5) | Ref | | | |
| Spring/river/well/stream/pond | 579 (37.2) | 49 (40.5) | 1.1 (0.8 – 1.7) | 0.476 | | |
| *Intervention* | | | | | | |
| No | 740 (47.6) | 60 (49.6) | Ref | | | |
| Yes | 816 (52.4) | 61 (50.4) | 0.9 (0.6 – 1.3) | 0.656 | 0.9 (0.6 – 1.4) | 0.716 |
| *Facility Delivery* | | | | | | |
| No | 482 (31.1) | 42 (34.7) | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Yes | 1070 (68.9) | 79 (65.3) | 0.8 (0.6 – 1.1) | 0.251 | | |
| **Maternal clinical characteristics** | | | | | | |
| *History of a small infant* | | | | | | |
| No | 218 (14.0) | 19 (15.7) | Ref | | | |
| Yes | 985 (63.3) | 68 (56.2) | 1.3 (0.7 – 2.1) | 0.386 | **2.1 (1.2 – 3.7)** | *0.014* |
| Prime gravida | *353 (22.7)* | 34 (28.1) | 1.4 (0.9 – 2.1) | 0.090 | 1.1 (0.6 – 1.8) | 0.778 |
| *Parity* | | | | | | |
| Prime gravida | 353 (22.7) | 34 (28.1) | Omitted | | | |
| 1-6 | 1043 (67.0) | 77 (63.6) | Ref | | | |
| 7 or more | 160 (10.3) | 10 ( 8.3) | 0.8 (0.5 – 1.5) | 0.573 | 0.6 (0.3 – 1.4) | 0.226 |
| *Maternal HIV infection* | | | | | | |
| No | 1455 (93.5) | 116 (95.9) | Ref | | | |
| Yes | 73 ( 4.7) | 5 ( 4.1) | 0.9 (0.4 – 2.0) | 0.723 | 0.9 (0.4 – 1.8) | 0.719 |
| Unknown | 28 ( 1.8) | 0 ( 0.0) | Not applicable | | | |
| *Antennal attendance* | | | | | | |
| No | 352 (22.6) | 30 (24.8) | Ref | | | |
| Yes | 1204 (77.4) | 91 (75.2) | 0.9 (0.6 – 1.3) | 0.522 | | |
| *IPT for malaria in pregnancy* | | | | | | |
| No | 704 (45.2) | 69 (57.0) | Ref | | | |
| Yes | 852 (54.8) | 52 (43.0) | 0.6 (0.4 – 0.8) | 0.003 | 0.6 (0.4 – 0.8) | 0.001 |
| *Malaria in pregnancy* | | | | | | |
| No | 502 (32.3) | 25 (20.7) | Ref | | | |
| Yes | 388 (24.9) | 32 (26.4) | 1.7 (1.01 – 2.7) | 0.046 | 1.7 (1.01 – 2.9) | 0.045 |
| Unknown | 666 (42.8) | 64 (52.9) | 1.9 (1.2 – 3.0) | 0.005 | 1.9 (1.1 – 3.2) | 0.020 |
| **Infant sex** | | | | | | |
| Female | 757 (48.7) | 63 (52.1) | Ref | | | |
| Male | 799 (51.3) | 58 (47.9) | 0.9 (0.6 – 1.2) | 0.393 | 0.9 (0.7 – 1.2) | 0.463 |

N/n (%) frequency (percentage), RR risk ratio, CI confidence interval, HIV human immunodeficiency virus

Infants born to mothers aged 35 or more years were two (adjusted RR 1.9 (95% CI: 1.1 –3.9) times more likely to be LBW compared to those born to mothers aged 20–34 years. A history of a small newborn in the second last pregnancy doubled the risk (aRR: 2.1, 95% CI: 1.2 – 3.4) of LBW compared to those without. A positive malaria test (aRR: 1.7, 95% CI: 1.01–2.9) or an unknown malaria status during pregnancy (aRR 1.9, 95% CI: 1.1 – 3.2) almost doubled the risk of LBW among the infants compared to those with known malaria negative tests. On the other hand, infants whose mothers received intermittent preventive treatment for malaria during pregnancy had a (aRR 0.6, 95% CI: 0.4 – 0.8) reduced risk of being LBW compared to those who did not. The integrated intervention package had no effect on the LBW in this post conflict setting of northern Uganda. These and more details are summarized in Table 3. Similarly, other known risk factors for LBW such as poverty, maternal education, teenage motherhood, grand multi–parity, ANC attendance and HIV infection were not associated with increased risks of LBW among mothers in the cohort.

*Preterm birth*

HIV infection was associated with and increased risk of PB (adjusted RR: 2.9, 95% CI: 1.1 – 7.3) in the multivariable analysis (Table 4). Maternal education (≥7 years) was associated with a reduced risk of PB (adjusted RR: 0.3, 95% CI: 0.1 – 0.98).

**Table 4. Bivariable and multivariable analysis of risk factors for preterm birth in northern Uganda.**

| Characteristics | All N=1279 n (%) | PB N=53 n (%) | Crude RR (95% CI) N=1279 | p value | Adjusted RR (95% CI) N=1279 | p value |
|---|---|---|---|---|---|---|
| **Maternal characteristics** | | | | | | |
| *Maternal age* | | | | | | |
| 12-19 years | 330 (25.8) | 18 (34.0) | 1.6 (0.9 – 2.9) | 0.142 | **2.0 (1.0 – 4.3)** | 0.050 |
| 20-34 years | 815 (63.7) | 28 (52.8) | Ref | | | |
| ≥35 years | 134 (10.5) | 7 (13.2) | 1.5 (0.7 – 3.5) | 0.295 | 1.2 (0.6 – 2.6) | 0.612 |
| *Maternal education* | | | | | | |
| 0-6 years | 1032 (80.7) | 50 (94.3) | Ref | | | |
| ≥7 years | 247 (19.3) | 3 ( 5.7) | 0.2 (0.1 – 0.8) | 0.022 | **0.3 (0.1 – 0.98)** | *0.047* |
| *Maternal vocational education* | | | | | | |
| No | 1131 (88.4) | 45 (84.9) | | | | |
| Yes | 148 (11.6) | 8 (15.1) | | | | |
| *Marital status* | | | | | | |
| Married | 1166 (91.2) | 47 (88.7) | 0.7 (0.3 – 1.5) | 0.393 | | |
| Single/separated/divorced/widowed | 113 ( 8.8) | 6 (11.3) | Ref | | | |
| *Wealth index* | | | | | | |
| Lower 40% | 574 (44.9) | 26 (49.1) | Ref | | | |
| Middle 40% | 465 (36.3) | 18 (34.0) | 0.8 (0.5 – 1.4) | 0.513 | 0.9 (0.6 – 1.5) | 0.815 |
| Upper 20% | 240 (18.8) | 9 (17.0) | 0.8 (0.4 – 1.9) | 0.650 | 1.1 (0.5 – 2.5) | 0.847 |
| *Father's occupation* | | | | | | |
| Farmer | 883 (69.0) | 38 (71.7) | Ref | | | |
| Employed | 274 (21.4) | 8 (15.1) | 1.4 (0.7 – 2.9) | 0.342 | | |
| Unemployed | 122 ( 9.5) | 7 (13.2) | 0.7 (0.4 – 1.4) | 0.305 | | |
| *Domestic water source* | | | | | | |
| Tap/Borehole | 802 (62.7) | 27 (50.9) | Ref | | | |
| Spring/river/well/stream/pond | 477 (37.3) | 26 (49.1) | 1.1 (0.8 – 1.7) | 0.476 | 1.5 (0.9 – 2.6) | 0.121 |
| *Intervention* | | | | | | |
| No | 601 (47.0) | 23 (43.4) | Ref | | | |
| Yes | 678 (53.0) | 30 (56.6) | 1.1 (0.6 – 2.1) | 0.670 | 1.2 (0.7 – 2.2) | 0.517 |
| *Facility Delivery* | | | | | | |
| No | 397 (31.0) | 23 (4.4) | Ref | | | |
| Yes | 882 (69.0) | 30 (56.6) | 0.6 (0.3- 1.01) | 0.054 | 0.6 (0.4 – 1.0) | 0.045 |
| **Maternal clinical factors** | | | | | | |
| *History of a small infant* | | | | | | |
| No | 964 (75.4) | 39 (73.6) | Ref | | | |
| Yes | 40 ( 3.1) | 2 ( 3.8) | 1.2 (0.2 – 5.7) | 0.927 | 1.0 (0.2 – 5.2) | 0.986 |
| Prime gravida | *275 (21.5)* | 12 (22.6) | 1.1 (0.5 – 2.0) | 0.884 | 0.8 (0.3 – 1.8) | 0.557 |
| *Parity* | | | | | | |
| Prime gravida | 275 (21.5) | 12 (22.6) | Ref | | | |
| 1-6 | 872 (68.2) | 34 (64.2) | 1.1 (0.6 – 2.1) | 0.790 | | |
| 7 or more | 132 (10.3) | 7 (13.2) | 1.4 (0.7 – 2.6) | 0.346 | | |
| *Maternal HIV infection* | | | | | | |
| No | 1205 (94.2) | 47 (88.7) | Ref | | | |
| Yes | 61 ( 4.8) | 6 (11.3) | 2.2 (0.9 – 5.6) | 0.094 | **2.9 (1.1 – 7.3)** | *0.026* |
| Unknown | 13 ( 1.0) | 0 ( 0.0) | NA | | | |
| *Antenatal attendance* | | | | | | |
| No | 283 (22.1) | 14 (26.4) | Ref | | | |
| Yes | 996 (77.9) | 39 (73.6) | 0.8 (0.4 – 1.4) | 0.451 | | |
| *IPT for malaria in pregnancy* | | | | | | |
| No | 695 (54.3) | 29 (54.7) | Ref | | | |
| Yes | 584 (45.7) | 24 (45.3) | 0.9 (0.5 – 1.6) | 0.832 | 1.0 (0.6 – 1.8) | 0.886 |
| *Malaria in pregnancy* | | | | | | |
| No | 330 (25.8) | 15 (28.3) | Ref | | | |
| Yes | 342 (26.7) | 13 (24.5) | 0.8 (0.5 – 1.5) | 0.568 | | |
| Unknown | 607 (47.5) | 25 (47.2) | 0.9 (0.5 – 1.6) | 0.785 | | |
| **Infant sex** | | | | | | |
| Female | 620 (48.5) | 20 (37.7) | Ref | | | |
| Male | 659 (51.5) | 33 (62.3) | 1.6 (0.9 – 2.7) | 0.117 | 1.6 (1.0 – 2.8) | 0.070 |

N/n (%) frequency (percentage), RR risk ratio, CI confidence interval, PB preterm birth, NA not applicable, IPT intermittent preventive treatment, HIV human immunodeficiency virus

## Discussion

In our cohort, 7.3% of infants were born low birthweight. Approximately, 4.1% of the infants were born preterm. Advanced maternal age (≥35 years), history of a small newborn in prior pregnancy, and malaria in pregnancy were associated with increased risk of LBW while intermittent preventive treatment of malaria (IPT) reduced it. Furthermore, maternal HIV infection was associated with an increased risk of PB while ≥7 years of formal education reduced it.

The proportion of LBW in our study in this area of Northern Uganda is lower than most other estimates, be it global, in sub-Saharan Africa, or in Uganda.[22,23] Several reasons may be advanced for these findings. Firstly, the methods used in the different studies may explain this difference. For instance, the global estimate is based on modelling limited data, where almost 50% of infants lack birthweight, including rural Uganda.[22] In our community cohort, 68% of infants were born in health facilities, while 32% were born at home; in this case, we may expect fewer LBW infants, compared to those born in health facilities, which receive mothers with complications. Likewise, a study done by Bater and colleagues in Northern and Western Uganda also reported lower rates, which may be due to the effects of food security and livelihood interventions among the studied mothers.[23] Thirdly, the inclusion criteria into the trial was a gestational age 28 or more weeks of pregnancy or any visibly pregnant woman. This implied that preterm births and low birthweight occurring before recruitment were systematically excluded, thus, we may have missed LBW and PB births in our source population. Our study is likely to have underestimated the true incidence of both LBW and PB. It should be noted that, throughout the study period, the pregnancy monitors (community recruiters) actively searched for pregnant mothers in each cluster and informed the study team. This means that, the only time we could have systematically excluded mothers who delivered before recruitment could have been in the first one to two of the recruitment exercise.

Factors associated with low birthweight included advanced maternal age ≥35 years, history of a small newborn in the previous pregnancy, maternal malaria in pregnancy and intermittent preventive treatment (IPT) for malaria. The finding that advanced maternal age (≥35 years) was associated with an increased risk of LBW in our cohort is not unique to our report. Numerous studies and meta-analyses have described the increased risk of LBW with low or advanced maternal age.[24] This may be due to increased risk of non-communicable diseases (NCDs) like hypertension, obesity, and diabetes with advanced maternal age.[24]

The study also reports an associated increased risk of LBW among mothers with history of a small newborn, in the most recent pregnancy. Other studies report similar links.[25] This may be due to the uncorrected effect of the causes of small newborns from the prior pregnancy, like maternal anaemia and malnutrition on subsequent pregnancy.

The relationship between malaria in pregnancy and its association with increased risk of LBW has been reported elsewhere.[26,27] Similarly, we also report a reduced risk of LBW among infants born to mothers who had intermittent preventive therapy for malaria during pregnancy. Malaria IPT during pregnancy reduces placental malaria, a long known risk factor for LBW and preterm births (small newborn).[28]

The PB proportion in our cohort was 5.0% and is similar to a hospital-based study in Eastern Uganda, with similar inclusion and exclusion criteria.[7] The observed estimate in this cohort, however, is lower than the global, sub-Saharan Africa, or Uganda estimates.[23,29]

The low PB proportion observed in our study may be due to the trial eligibility criteria discussed above that could have resulted in exclusion of some preterm births occurring before recruitment into the main trial. Secondly, the NBS for foetal maturation for gestational age determination (instead of mid-pregnancy ultrasound as the gold standard), may have contributed to the underestimation of PB in this cohort. For instance, a study by Sasidharan and colleagues reported that NBS overestimated gestational age (GA) by up to 2 weeks (8 MRTS), with increasing postnatal age.[30] Therefore, if the current global PB modelled estimates by the global burden of disease (GBD) research group are true, we may have over-estimated GA by 3MRTS (1.2 weeks), see our sensitivity analysis in Table 2. Although scientists modified the NBS system to identify extremely preterm babies up to seven days of postnatal age, it seems postnatal age at assessment may have played a role and resulted in the observed low PB estimates in our cohort. This is because, we excluded 363/1833 (19.8%) infants not reached for NBS gestational age (GA) assessment within 7 days of postnatal life, and another 191/1833 (10.4%) of the infants without birthweight within 48 hours of postnatal age.

Despite the challenges faced in PB diagnosis in our setting, the findings may still be relevant in contributing to the pool of knowledge on preterm births and associated risk factors, to guide decision making in a resource-limited post-conflict setting. This is because, any study with preterm births proportion above 3%, the minimum cut off for PBs among healthy mothers by INTERGROWTH, is included in the global estimating preterm birth by the Global Burden of Disease (GBD) working groups.[6,29] Besides, the finding is similar to the preterm birth proportion, based on history of preterm birth in the second last pregnancy, among the same cohort of mothers, albeit the recall bias. Lastly, but equally relevant, the overall proportion of infants who are both LBW and PB to live births of 1.5%, was similar to that reported in Kenya (1.2%), though lower than the estimated 5.5%.[31]

The factor that was associated with an increased risk of preterm birth was maternal HIV infection. The increased risk of PBs among HIV infected women, compared to the uninfected has also been documented over the last three decades.[32] The mechanism of HIV infection causing PB are many, but like any other infectious diseases, the release of pro-inflammatory cytokines may stimulate uterine contraction, leading to preterm labour and birth.[33] In addition, opportunistic infections and the use of protease inhibitors (PIs) based regimen in the first trimester, may also increase the risk of PB.[34] As reported in another recent study, spontaneous PB may also result from vaginal and not systemic inflammation among HIV infected, compared to those not.[35]

Maternal education for seven or more years was associated with a reduced risk of PB compared to 0-6 years of formal education. Our finding that low maternal education is associated with an increased risk of PB has been reported elsewhere.[36-38]

In our cohort, teenage motherhood doubled the risk of PB and this is of public health importance. The finding is similar to findings from several other studies across the globe.[39,40] Although the biological link between teenage pregnancy and PB is not properly understood,[12,41] pregnant teens are likely to be disfavoured in several aspects such as education, access to care and nutrition compared to older mothers.[42-44]

The study also reported an increased risk of PB among male infants, compared to female infants. This may be a methodological artefact due to differences in NBS scoring of the two sexes. An analysis of mean difference for the overall MRTS and individual elements for physical and neuromuscular scores by sex, demonstrated a difference in physical maturity rating for breasts. Female infants were systematically over-scored by a mean difference of 0.14, 95% CI: 0.08 – 0.21 points (4 days, 95% CI: 2 – 6) in the physical maturity rating for breasts, which may contribute to fewer infants being classified as being PB. It is still possible that there is still a true increase in the risk of PB for male infants as this has been reported elsewhere.[19,45]

**Limitations and strengths**

The main limitation of our study is the potential for selection bias at inclusion which may have introduced systematic error. In the main Survival Pluss randomised trial in which our observational study was nested, inclusions were allowed at any time from 28 or more weeks of gestation. It means that a pregnant woman could be included at, for instance, at 35 weeks of gestation. This also means that not all pregnant women in the study area were followed up from exactly 28 weeks of gestation. Women who had LBW and PB before recruitment into the trial were systematically excluded from our study. This likely caused us to underestimate the true incidence of LBW and PB. This could explain the low incidence of LBW and PB reported in this study.
Furthermore, additional selection biases could have occurred due to loss to follow-up resulting from missing birthweight and/or gestational age assessment (GA) of the infants. For the PB, we restricted the analysis to the sample of infants with both GA and birthweight. Approximately 598 of infants (31.9%) of the 1877 in the cohort did not have both birthweight and gestational age measurements and were excluded from the analysis. This could have possibly resulted in a selection bias. That said, in a

sensitivity analysis, we found no major differences in socio-demographic characteristics of included and excluded participants. Future studies to estimate the incidence of LBW and PB should aim at enrolling mothers in the first trimester, ensure ultrasound scans for GA estimation and following up the entire cohort for the remainder of the pregnancy. This would permit more accurate gestational age estimations and provide a more complete cohort.

Albeit the above limitations, there were several strengths in our study. Firstly, we used a community-based cohort – likely to reflect the community at large. Secondly, we were able to follow-up and obtain birthweight within 48 hours on 1556/1877 (82.9%) of the cohort, minimising the risk of selection bias. Thirdly, mothers were interviewed shortly after the delivery, minimising the likelihood of recall bias. Lastly, we used hard, explicitly defined outcome measures (low birthweight and preterm birth – albeit the limitations of NBS). This might have reduced the likelihood of misclassification/information bias.

## Conclusions

The incidence of LBW and PB were low, compared to the national, sub-Saharan Africa and global estimates – possibly due to methodological limitations. Advanced maternal age ≥ 35 years and history of a small newborn were associated with increased risk of low birthweight. Maternal formal education for ≥7 years was associated with a reduced risk of LBW and PB while HIV infection was associated with an increased risk of PB.

## Recommendations

In order to obtain reliable results on the proportion of preterm births in future community-based studies, it is paramount to identify pregnant mothers early in pregnancy, and to record gestational age by antenatal ultrasound. If assessment of intrauterine growth restriction is included, expertise in Doppler ultrasonography is required. Context-specific assessment of the causes of intra-uterine growth restriction and of modifiable risk factors, such as hypertension, may also be required in order to enable evidence-based interventions.

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# II

III

Tropical Medicine and Health

RESEARCH Open Access

# Prevalence and factors associated with neonatal hypoglycemia in Northern Uganda: a community-based cross-sectional study

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## Abstract

**Background:** Neonatal hypoglycemia is the most common endocrine abnormality in children, which is associated with increased morbidity and mortality. The burden and risk factors of neonatal hypoglycemia in rural communities in sub-Saharan Africa are unknown.

**Objective:** To determine the prevalence and risk factors for neonatal hypoglycemia in Lira District, Northern Uganda.

**Methods:** This was a community-based cross-sectional study, nested in a cluster randomized controlled trial designed to promote health facility births and newborn care practices in Lira District, Northern Uganda. This study recruited neonates born to mothers in the parent study. Random blood glucose was measured using an On Call® Plus glucometer (ACON Laboratories, Inc., 10125 Mesa Road, San Diego, CA, USA). We defined hypoglycemia as a blood glucose of < 47 mg/dl. To determine the factors associated with neonatal hypoglycemia, a multivariable linear regression mixed-effects model was used.

**Results:** We examined 1416 participants of mean age 3.1 days (standard deviation (SD) 2.1) and mean weight of 3.2 kg (SD 0.5). The mean neonatal blood glucose level was 81.6 mg/dl (SD 16.8). The prevalence of a blood glucose concentration of < 47 mg/dl was 2.2% (31/1416): 95% CI 1.2%, 3.9%. The risk factors for neonatal hypoglycemia were delayed breastfeeding initiation [adjusted mean difference, − 2.6; 95% CI, − 4.4, − 0.79] and child age of 3 days or less [adjusted mean, − 12.2; 95% CI, − 14.0, − 10.4].

**Conclusion:** The incidence of neonatal hypoglycemia was low in this community and was predicted by delay in initiating breastfeeding and a child age of 3 days or less. We therefore suggest targeted screening and management of neonatal hypoglycemia among neonates before 3 days of age and those who are delayed in the onset of breastfeeding.

**Keywords:** Hypoglycemia, Newborn care, Breastfeeding, Neonatal care, Endocrinology

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## Introduction

Neonatal hypoglycemia, defined differently by various authors as random blood sugars ranging from 18 to 72 mg/dl [1–3], is the most common metabolic abnormality in newborns and results in increased morbidity and mortality [1, 4, 5]. The risk of neonatal hypoglycemia is particularly high in preterms, low birth weight neonates, and neonates born to diabetic mothers [1, 6]. Ironically, neonates commonly develop transient hypoglycemia in the first few hours of life as a normal physiological process [3, 7]. However, some neonates progress to a severe and prolonged form of neonatal hypoglycemia, which can result in seizures and poor neuro-developmental outcomes if poorly managed [1, 3].

Currently, there is no consensus on the appropriate glucose cutoff value that differentiates transient hypoglycemia from the prolonged pathological form of neonatal hypoglycemia [3]. Various authors have suggested cutoff levels ranging from 47 to 60 mg/dl [2, 3]. The proposed cutoffs may not be applicable to newborns in sub-Saharan Africa that are breastfed early, and for longer periods [8]. Moreover, practices such as immediate umbilical cord clamping [9] and home births are common in some parts of sub-Saharan Africa [10], which may result in differing incidence and outcomes of neonatal hypoglycemia. Whereas transient neonatal hypoglycemia in the first 48 h is often inconsequential [3, 7], there is some evidence that a single episode of transient hypoglycemia may result in neuro-developmental abnormalities [11].

Although universal screening of asymptomatic and low-risk neonates for hypoglycemia may be unnecessary and harmful [3, 12], there is evidence that asymptomatic hypoglycemia could result in neuro-developmental abnormalities in up to 20% of affected neonates [13, 14]. Moreover, context-specific risk factors in rural communities in sub-Saharan Africa that could guide screening are unknown.

We therefore aimed to determine the incidence and risk factors of neonatal hypoglycemia in the first 7 days of life in a rural community in Northern Uganda to enable development of contextually relevant screening guidelines for neonatal hypoglycemia.

## Materials and methods

### Study design

This was a community-based cross-sectional study of neonates born to women enrolled in a cluster randomized controlled trial evaluating the effect of peer counseling on health facility births (Survival Pluss study registered on ClinicalTrial.gov as NCT02605369).

### Study setting

The study was conducted in Lira District, Northern Uganda, between January 2018 and March 2019. Lira District is approximately 340 km from the capital city, Kampala, and has 13 sub-counties, 1 municipality, and 751 villages. We recruited from Aromo, Agweng, and Ogur sub-counties located in the northern part of the district. These sub-counties were chosen because they were to be the site of the parent study. At the time of the study, the population of Lira District is ~ 400,000 people. The majority of the people lived in rural areas and practice subsistence farming [15]. The Uganda Demographic and Health Survey conducted in 2016 reported that ~ 29 of every 1000 newborns died in the first 28 days of life in the region covering the Lira District [16].

### Survival Pluss study (the parent study)

The parent study was a community-based cluster randomized controlled trial designed to evaluate the effect of a combined intervention on the proportion of mothers giving birth in health facilities. The combined intervention consisted of peer counseling, mobile phone messaging, and distribution of mama kits. The unit of randomization was a cluster, made up of 5 to 10 villages with a population of > 1000 people. Up to 30 clusters were randomized (ratio of 1:1) to the intervention or control arm. Mothers were enrolled in the third trimester of pregnancy and followed up for 50 days postpartum. Each village had a recruiter (pregnancy monitor) who was elected during a community meeting and who notified the research team of all pregnant women in her village during the study period and of all births. During home visits, research assistants recruited women of 28 or more weeks pregnant who were resident in the selected clusters. They were followed up on days 1, 7, 28, and 52 postpartum.

### Study participants

All newborns of mothers participating in the cluster randomized controlled trial, who were alive on the day of examination, within 1 week of birth, and whose guardians consented to a glucose measurement, were eligible for the study. Severely ill neonates who were admitted to hospitals at the time of the study were excluded.

### Study procedure

Trained midwives visited the mother as soon after birth as possible, but no later than 1 week after birth, and obtained a random blood sugar by pricking the newborn's heel. Random blood glucose was measured in mmol/l using an On Call® Plus glucometer (ACON Laboratories, Inc., 10125 Mesa Road, San Diego, CA, USA), a point-of-care test. Under aseptic conditions, we obtained blood samples from the heels of neonates. The heel was first cleaned with alcohol swabs and dried with cotton. A single-use safety lancet was used to prick the heel.

Maternal random blood glucose was also obtained at the same time from a finger prick. The team was closely supervised by a pediatric endocrinologist and a medical doctor who had trained them on sample collection, observed their initial procedures, and occasionally sitting in during the recruitment visits to ensure the standard operating procedures were followed.

### Study variables

To determine risk factors for neonatal hypoglycemia, we analyzed neonatal blood glucose as a continuous outcome. To determine short-term outcomes of neonatal hypoglycemia, we used a categorized neonatal blood glucose measurement. A cutoff of < 47 mg/dl was used, as it was most commonly used in prior studies and is not that different from more recent suggestions [2, 3, 17–19]. We, however, also investigated cutoffs of < 60 mg/dl and < 70 mg/dl [3]. Data was collected on several risk factors during pregnancy and immediately after birth. This included maternal age, parity, maternal education, paternal education, wealth, singleton or multiple birth, sex of the newborn, place of birth, birth weight, early breastfeeding initiation, bathing of the newborn, maternal BMI, age of baby, and the place the newborn was immediately after birth. Wealth quintiles were calculated from an asset-based index using principal component analysis [20], based on ownership of assets in the household, including mobile phone, radio, land, cupboard, bicycle, motorcycle, and assessing the household dwelling characteristics—material of the floor, roof, and wall. We defined early breastfeeding initiation as the initiation of breastfeeding within 1 h of birth and delayed breastfeeding initiation as the initiation of breastfeeding later than 1 h after birth. Low birth weight was defined as being < 2.5 kg.

### Power and sample size

The sample size was limited by the size of the parent study. We enrolled 1416 neonates who were part of the parent cluster randomized trial. This sample size results in an absolute precision of 1.2 to 4.4%, i.e., the difference between the point estimate and the 95% confidence interval (CI) for incidence values ranging from 2 to 50%.

### Data analysis

We summarized categorical variables as proportions and continuous variables as means (SD) or medians (IQR) and compared them using Student's $t$ tests or Mann-Whitney $U$ tests as appropriate. The prevalence of neonatal hypoglycemia was defined as blood glucose < 47 mg/dl. We used linearized variance estimation adjusting for clustering to compute the confidence intervals around the estimates. To determine the factors associated with neonatal hypoglycemia, a multivariable linear regression mixed-effects model was used in which the random effect was the cluster. Based on scientific literature and biological plausibility, the following covariates were added to the fixed effects part of the model, low birth weight, delayed breastfeeding initiation, bathing of the baby in the first 24 h, maternal hyperglycemia (blood glucose ≥ 198 mg/dl), any maternal complication during birth, maternal age, maternal education, parity, place of birth, wealth index, and cesarean section. Since this study was nested in a cluster randomized controlled trial, the trial arm was added as a fixed effect. We assumed an exchangeable correlation and used maximum likelihood estimation in fitting the model. All analyses were done using STATA 14.0 (StataCorp, College Station, TX, USA).

### Ethical considerations

Ethical approval for the study was obtained from the following bodies: (1) Research and Ethics committee School of Medicine, Makerere University (SOMREC: REF 2015-121); (2) Uganda National Council of Science and Technology (UNCST: SS 3954); and (3) Regional Committees for Medical and Health Research Ethics (REK VEST 2017/2079). We obtained written informed consent from the caretakers of all participants in the study. Participants whose neonates were hypoglycemic were encouraged to breastfeed immediately and, when necessary, a referral to the nearest health facility was facilitated.

## Results

### Participant characteristics

We examined 1416 participants (Fig. 1). The mean age of participants was 3.1 days (standard deviation (SD) 2.1). The mean weight of the participants was 3.2 kg (SD 0.5). The average age of their mothers was 24.7 years (6.8). Further characteristics are given in Table 1.

### Proportion of neonates with hypoglycemia in the first 7 days of life

The mean neonatal blood glucose level was 81.6 mg/dl (SD 16.8), and the median blood glucose 81 (IQR 70.2, 93.6). The prevalence of a blood glucose concentration < 47 mg/dl was 2.2% (31/1416): 95% CI 1.2%, 3.9%.

### Risk factors for neonatal hypoglycemia

The risk factors for neonatal hypoglycemia were delayed breastfeeding initiation, bathing the baby in the first 24 h after birth, and the baby's age 3 days or younger at examination. Mean blood glucose levels were 2.6 mg/dl lower among neonates who were breastfed later than 1 h compared to those who were breastfed in the first hour after birth [adjusted mean difference, − 2.6; 95% CI, − 4.4, − 0.79]. Neonates bathed within the first 24 h after birth had on average 2.3 mg/dl higher glucose

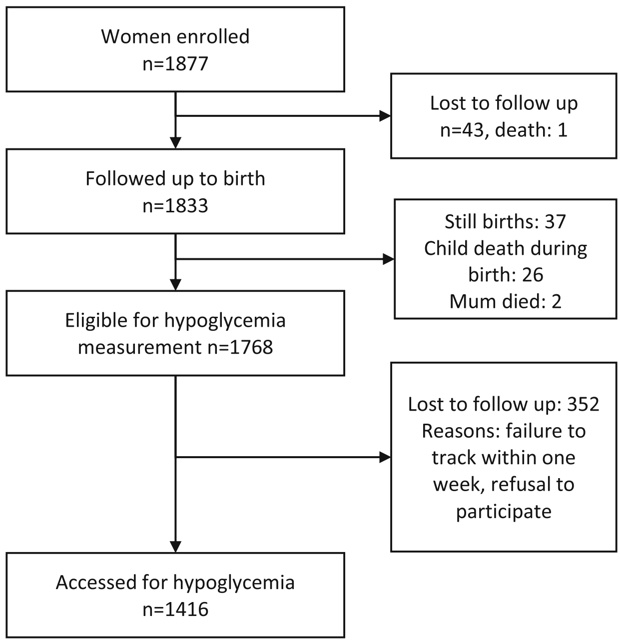


**Fig 1** Study profile of neonates assessed for hypoglycemia in Lira District, Northern Uganda

concentration than those who were bathed afterwards [adjusted mean 2.3; 95% CI, 0.46, 4.2]. At the time of examination, neonates 3 days old or younger had an average of 12.2 mg/dl lower glucose concentration than those over 3 days [adjusted mean, − 12.2; 95% CI, − 14.0, − 10.4] (Table 2, Fig. 2).

## Discussion

The prevalence of neonatal hypoglycemia in the first week of life was low (2.2%). The mean random blood glucose of our sample population was 82.1 mg/dl (SD 17.5), which is much lower than reported by others [21–24], possibly for two reasons. First, our population had high levels of early breastfeeding initiation and continued breastfeeding [16]. Since breastfeeding prevents and resolves neonatal hypoglycemia [1, 3], the neonates who could or might have suffered from neonatal hypoglycemia were promptly managed. Second, the study population had a very low prevalence of maternal hyperglycemia (a marker of diabetes mellitus) and low birth weight (a marker of prematurity). This corresponds to findings from a nationwide survey in Uganda that reported a prevalence of impaired fasting glycemia of 2% [25]. Since maternal hyperglycemia is one of the causes of neonatal hypoglycemia [3], the low population prevalence could partly explain the low prevalence of it in our selected population. Nonetheless, our findings are similar to those obtained from two American and one Indian study [26–28].

Delayed breastfeeding initiation was associated with neonatal hypoglycemia. This finding is not surprising, and it has been reported by previous authors [21, 28, 29]; breastfeeding is an initial means of correcting neonatal hypoglycemia [1]. This finding reinforces the need to encourage mothers to breastfeed their babies within the first hour after birth. It also sheds light on a potential mechanism through which delayed breastfeeding could increase the risk of neonatal morbidity and mortality [30].

Bathing the newborn within 24 h after birth was also associated with neonatal hypoglycemia. This can be explained by the fact that bathing newborns within 24 h of birth predisposes them to cold stress and hypothermia [31], which are risk factors for neonatal hypoglycemia [28]. However, in our study sample, the association between hypothermia and hypoglycemia was very weak and imprecise. As such, the association between bathing the newborn within 24 h and hypoglycemia could be non-casual. This non-causal association could result from both neonatal hypoglycemia and bathing newborns within 24 h after birth causing neonatal hypothermia [32]. This would result in a conditional association between neonatal hypoglycemia and bathing the newborn within 24 h after birth. We therefore suggest that this

**Table 1** Characteristics of newborns assessed for hypoglycemia in Northern Uganda

| Variable | Frequency ($n$ = 1416) | Percentage |
|---|---|---|
| **Mother's age** | | |
| ≤ 19 | 369 | 26.1 |
| 20-30 | 760 | 53.7 |
| > 30 | 287 | 20.3 |
| **Mother's education** | | |
| None | 184 | 13 |
| Primary | 1107 | 78.2 |
| Secondary | 107 | 7.6 |
| Tertiary | 18 | 1.3 |
| **Father's education** | | |
| None | 25 | 1.8 |
| Primary | 843 | 59.5 |
| Secondary | 347 | 24.5 |
| Tertiary | 77 | 5.4 |
| Missing | 124 | 8.8 |
| **Parity** | | |
| ≤ 1 | 637 | 45 |
| 2-4 | 484 | 34.2 |
| > 4 | 295 | 20.8 |
| **Place of birth** | | |
| Home | 464 | 32.8 |
| Health facility | 951 | 67.2 |
| Missing | 1 | 0.1 |
| **Cesarean section** | | |
| No | 1380 | 97.5 |
| Yes | 36 | 2.5 |
| **Marital status** | | |
| Single | 124 | 8.8 |
| Married | 1292 | 91.2 |
| **Electricity** | | |
| No | 1262 | 89.1 |
| Yes | 154 | 10.9 |
| **Delayed or no cry** | | |
| No | 1347 | 95.1 |
| Yes | 69 | 4.9 |
| **Birth weight** | | |
| Normal | 1153 | 81.4 |
| Low birth weight | 75 | 5.3 |
| Missing | 188 | 13.3 |
| **Phone in home** | | |
| No | 623 | 44 |
| Yes | 793 | 56 |

**Table 1** Characteristics of newborns assessed for hypoglycemia in Northern Uganda *(Continued)*

| Variable | Frequency ($n$ = 1416) | Percentage |
|---|---|---|
| **Wealth index** | | |
| Poorest | 286 | 20.2 |
| 2 | 349 | 24.6 |
| 3 | 268 | 18.9 |
| 4 | 243 | 17.2 |
| Richest | 270 | 19.1 |
| **Oxygen administered** | | |
| No | 1402 | 99.0 |
| Yes | 13 | 0.9 |
| Missing | 1 | 0.1 |
| **Bathed baby in first 24 h** | | |
| No | 591 | 41.7 |
| Yes | 820 | 57.9 |
| Missing | 5 | 0.4 |
| **Maternal antenatal BMI** | | |
| < 18.5 | 11 | 0.8 |
| 18.5-24.9 | 1174 | 83.7 |
| 25-29.9 | 194 | 13.7 |
| ≥ 30 | 24 | 1.7 |
| Missing | 13 | 0.9 |
| **Maternal hyperglycemia** | | |
| No | 1393 | 98.4 |
| Yes | 23 | 1.6 |
| **Breastfeeding initiation** | | |
| Late | 530 | 37.4 |
| Early | 876 | 61.9 |
| Missing | 10 | 0.7 |

association could result from a form of collider bias [32–35].

Neonates of 3 days or younger had lower blood glucose concentrations compared to older ones. The incidence of neonatal hypoglycemia decreases as the child ages [21], which might explain this difference. This is because physiological transitional hypoglycemia resolves within the first 48-72 h, after which blood neonatal blood glucose levels gradually increase [3, 22].

## Limitations

Our study had some limitations. First, our loss to follow-up and inability to reach some neonates within the first week of life might have resulted in selection bias. Since we did not examine hospitalized neonates, who might have had lower blood glucose values than healthier neonates, we could have underestimated the burden of neonatal hypoglycemia. Second, we could only take one

**Table 2** Risk factors of neonatal hypoglycemia in Northern Uganda

| | Bivariable<br>Unadjusted mean difference (95 mg/dl% CI) | Multivariable<br>Adjusted mean difference (95% CI) |
|---|---|---|
| **Intervention group** | | |
| Control | 0 | 0 |
| Intervention | − 1.6 (− 4.1, 0.84) | − 1.2 (− 3.4, 0.99) |
| **Maternal hyperglycemia** | | |
| No | 0 | 0 |
| Yes | − 0.61 (− 7.5, 6.3) | − 0.22 (− 7.2, 6.7) |
| **Age of neonate** | | |
| > 3 days | | 0 |
| ≤ 3 days | − 12.9 (− 14.5, − 11.2) | **− 12.2 (− 14.0, − 10.4)** |
| **Maternal antenatal BMI** | | |
| < 18.5 | 1.1 (− 8.9, 11.0) | 1.1 (− 8.0, 10.2) |
| 18.5-24.9 | 0 | 0 |
| 25-29.9 | 0.37 (− 2.2, 2.9) | 1.7 (− 0.96, 4.3) |
| ≥ 30 | − 0.56 (− 7.3, 6.2) | − 0.37 (− 7.3, 6.6) |
| **Low birth weight (less than 2.5 kg)** | | |
| No | 0 | 0 |
| Yes | − 0.76 (− 4.6, 3.1) | 0.48 (− 3.1, 4.1) |
| **Bathed baby before visit** | | |
| No | 0 | 0 |
| Yes | 4.8 (3.0, 6.6) | **2.3 (0.46, 4.2)** |
| **Breastfeeding initiation** | | |
| Early | 0 | 0 |
| Late | − 2.4 (− 4.2, 0.57) | **− 2.6 (− 4.4, − 0.79)** |
| **Maternal complications during pregnancy** | | |
| No | 0 | 0 |
| Yes | 1.1 (− 0.65, 2.9) | − 1.2 (− 3.5, 1.1) |
| **Neonatal hypothermia** | | |
| No | 0 | 0 |
| Yes | − 1.4 (− 3.8, 1.1) | − 1.2 (− 3.5, 1.1) |
| **Age of mother** | | |
| ≤ 19 | 0 | 0 |
| 20-30 | 1.6 (− 0.50, 3.7) | 0.76 (− 1.3, 2.9) |
| > 30 | 0.30 (− 2.2, 2.9) | − 0.02 (− 2.8, 2.7) |
| **Mother's education** | | |
| None | 0 | 0 |
| Primary | 1.2 (− 1.4, 3.8) | 0.60 (− 2.1, 3.3) |
| ≥ Secondary | 1.7 (− 2.1, 5.5) | 1.0 (− 3.0, 5.0) |
| **Place of birth** | | |
| Health facility | 0 | 0 |
| Home | 1.3 (− 0.65, 3.1) | − 0.20 (− 2.2, 1.8) |
| **Wealth quintiles** | | |
| 1 (poorest) | 0 | 0 |
| 2 | − 0.72 (− 3.3, 1.9) | − 0.63 (− 3.2, 2.0) |
| 3 | − 1.4 (− 4.2, 1.4) | − 1.7 (− 4.4, 1.1) |
| 4 | − 0.52 (− 2.4, 3.4) | 0.11 (− 2.8, 3.0) |
| 5 (richest) | − 0.30 (− 3.1, 2.5) | − 0.93 (− 3.8, 1.9) |

blood glucose measurement, which could have resulted in a lower estimate of neonatal hypoglycemia. We recommend that future studies take repeated blood sugar measurements if possible. Finally, we did not obtain information on the last time the child was breastfed prior to blood glucose sampling, or on the consumption of products such as tea and herbs prior to our test.

## Conclusion

The incidence of neonatal hypoglycemia was low in this community and was predicted by delayed breastfeeding initiation and child age of 3 days or less. We therefore suggest targeted screening and management of neonatal hypoglycemia among neonates younger than 3 days and those who experience delay in breastfeeding initiation.

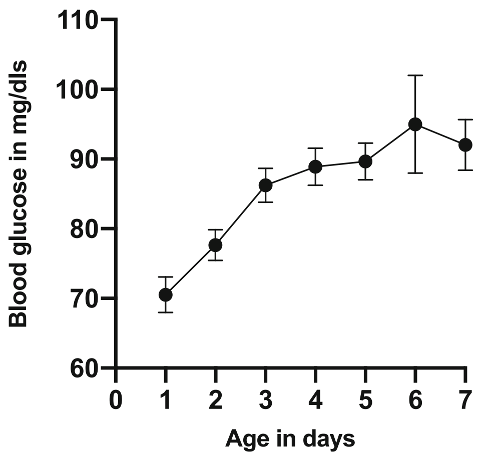


**Fig. 2** Mean blood glucose, with 95% confidence intervals, of neonates from the age of 1 to 7 days in Northern Uganda

### Abbreviations
SD: Standard deviation; BMI: Body mass index; CI: Confidence interval; IQR: Inter-quartile range; UNCST: Uganda National Council of Science and Technology


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### Authors' contributions
DM, BO, TP, SK, JKT, VN, GN, and TT conceived, designed, and supervised the study; analyzed the data; and wrote the first draft of manuscript. TP, JD, CB, and SK were instrumental in the data analysis and drafting of the final manuscript. All authors read and approved the final version of the manuscript.


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### Availability of data and materials
The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate
Ethical approval to conduct the study was obtained from the following bodies: (1) Research and Ethics committee School of Medicine, Makerere University (SOMREC: REF 2015-121); (2) Uganda National Council of Science and Technology (UNCST: SS 3954); and (3) Regional Committees for Medical and Health Research Ethics (REK VEST 2017/2079). We obtained written informed consent from the caretakers of all participants in the study. Participants whose neonates were found to have hypoglycemia were encouraged to breastfeed immediately and, when necessary, referred to the nearest health facility.

### Consent for publication
Not applicable

### Competing interests
All authors declare no conflict of interest.


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# Adding video-debriefing to Helping-Babies-Breathe training enhanced retention of neonatal resuscitation knowledge and skills among health workers in Uganda: a cluster randomized trial

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# Adding video-debriefing to Helping-Babies-Breathe training enhanced retention of neonatal resuscitation knowledge and skills among health workers in Uganda: a cluster randomized trial

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**ABSTRACT**

**Background:** Skilled birth attendants must be competent to provide prompt resuscitation to save newborn lives at birth. Both knowledge and skills (competence) decline with time after training but the optimal duration for refresher training among frontline-skilled birth attendants in low-resource settings is unknown.
**Objectives:** We assessed the effect of an innovative Helping-Babies-Breathe simulation-based teaching method using video-debriefing compared to standard Helping-Babies-Breathe training on 1) neonatal resuscitation knowledge and skills attainment and 2) competence retention among skilled birth attendants in Northern Uganda.
**Methods:** A total of 26 health facilities with 86 birth attendants were equally randomised to intervention and control arms. The 2nd edition of the American Association of Pediatrics Helping-Babies-Breathe curriculum was used for training and assessment. Knowledge and skills were assessed pre- and post-training, and during follow-up at 6 months. A mixed effects linear regression model for repeated measures was used to assess the short and long-term effects of the intervention on neonatal resuscitation practices while accounting for clustering.
**Results:** Eighty-two (95.3%) skilled birth attendants completed follow-up at 6 months. Approximately 80% of these had no prior Helping-Babies-Breathe training and 75% reported practicing neonatal resuscitation routinely. Standard Helping-Babies-Breathe training with video-debriefing improved knowledge and skills attainment post-training [adjusted mean difference: 5.34; 95% CI: 0.82–10.78] and retention [adjusted mean difference: 2.97; 95% CI: 1.52–4.41] over 6 months post-training compared to standard training after adjusting for confounding and clustering. Factors that reduced knowledge and skills retention among birth attendants were monthly resuscitation of one neonate or more and being in service for more than 5 years.
**Conclusion:** Adding video-debriefing to standard Helping-Babies-Breathe training had an effect on birth attendants' competence attainment and retention over 6 months in Uganda. However, more research is needed to justify the proposed intervention in this context.

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Video-debriefing; Helping-Babies-Breathe; standard training; knowledge and skills; attainment and retention

## Background

Despite the global effort to improve knowledge and skills among frontline-skilled birth attendants (SBAs), the reduction in neonatal mortality – especially in low-resource settings including Uganda – has been modest [1]. Uganda is committed to the global Sustainable Development Goal (SDG) 3.2 of reducing neonatal mortality to <12 per 1000 live births by 2030. To achieve this, innovation and creativity in training methods are needed. Methods such as video-debriefing can potentially enhance neonatal resuscitation knowledge and skills attainment, and retention among SBAs.

Debriefing is a process of information stimulus and response used by highly skilled professionals working in high-risk industries such as aviation, army, and health-care systems, to improve behaviour or performance and promote clients and patients' safety [2,3]. Video-debriefing is the use of post-event video recordings to facilitate debriefing and learning among frontline SBAs. An SBA is a formally trained health-worker who provides skilled care to pregnant mothers during delivery.

Globally, about 10% of neonates require support to establish breathing at birth. Of these, >90% can be saved with low-cost interventions, such as the Helping-Babies-Breathe (HBB) training program. The HBB program is simulation-based training that utilizes neonatal simulators known as NeoNatalie manikin (Laerdal Global, Stavanger, Norway) to impart neonatal resuscitation

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knowledge and skills among SBAs in low-resource settings [1]. The 2nd edition of the standard American Association of Pediatrics (AAP) HBB curriculum consists of principles of basic neonatal resuscitation, a multiple-choice questionnaire (MCQ) on knowledge, and bag-mask ventilation (BMV) and objective structured clinical examinations A and B (OSCE-A & B) skills checklists [4,5].

Since the introduction of the HBB programme in 2010, many SBAs in low-resource settings have been trained and thousands of newborn babies have received neonatal resuscitation. While many studies have documented a decline in knowledge and skills with time after HBB training, the rate of knowledge and skills decline and the optimal timing for instituting refresher training are unknown [6–8].

Furthermore, several studies demonstrate conflicting benefits of the HBB training program to the attained knowledge and skills of neonatal care practices and survival. A study in Tanzania showed no knowledge and skills translation into neonatal care practice post-training [9]. A systematic review reported improved neonatal survival within the first 24 h of life but was unsustained at 28 days of life [10]. The relative rarity of birth asphyxia and the opportunity to practice neonatal resuscitation skills by trained SBAs may explain this paucity of knowledge and skills [11,12]. A randomized trial of a booster training strategy by hands-on or video trainings at 3–5 months among resident physicians in the United States of America (USA) showed no beneficial effects regarding the retention of knowledge and skills [13], while evidence from a longitudinal study in the Sudan showed that regular manikin practice was associated with skills retention among village midwives one year after training [14].

In view of the conflicting findings above, we hypothesized that a cluster-randomized trial of an innovative teaching method of adding video-debriefing to standard neonatal resuscitation training compared with standard training alone would improve knowledge and skills attainment and retention among SBAs in Lira district, northern Uganda, over a 6 months' follow-up period. The main objectives of the study were to: 1) assess the effect of standard HBB training with video-debriefing compared with standard training alone on SBAs' knowledge and skills attainment immediate post-training and 2) estimate the effect of this modified teaching method on knowledge and skills retention over 6 months' period after training.

## Methods

We conducted a cluster-randomized trial of 26 health facility (HF) clusters (18 public and 8 private) conducting deliveries in Lira District, Northern Uganda, over a 6-month follow-up period. The district has a low proportion of health facility deliveries (<60%), and a high neonatal mortality (30/1000 live births, above the national average of 19/1000) [15]. A total of 86 SBAs from 26 HF clusters were trained in June 2018 and followed-up for 6 months from July 2018 to January 2019. A cluster design was deemed appropriate to study interventions that target a group of SBAs from the same institution with similar characteristics and behaviour while controlling for cross contamination across individuals from the same facility, had they been individually randomized.

### *Sample size for clusters*

To calculate the number of clusters, we assumed a fixed number of clusters, minimal intra-cluster variability, variable cluster sizes (2 to 6 SBAs each), and minimum sample size to detect a 30% difference in competence (knowledge and skills) between intervention and control arms. Adding 20% loss to follow up, a total of 26 clusters (13 in each arm), were deemed adequate [16].

*Sampling*: All trial participants providing delivery and neonatal care were selected per cluster to participate in the training using the population proportional to sample size. Most facilities, however, had between 2 and 6 SBAs. In such cases, all were included in the training program.

Restricted randomization, allocation concealment, and blinding were done by a statistician who was not part of the study. The clusters were randomized into intervention and control arms in a ratio of 1:1. The assessors/research assistants were blinded to the intervention allocations, but the study participants, the principal investigator (PI) and trainers knew the group on the day of the training. The PI and assessment team were blinded to the HF intervention allocation throughout the follow-up period, by the data manager who kept the randomization codes. This controlled both performance and assessment bias.

### *Inclusion and exclusion criteria*

We included HFs and SBAs providing delivery and newborn care services. Community vaccinators and laboratory technicians who turned up for training and were neither providing delivery nor newborn care were excluded.

## Description of interventions

The control arm received standard HBB training alone. The intervention arm received video-debriefing in addition to the standard HBB training.

### *The control (standard HBB training) arm*

International, national and regional HBB facilitators trained the SBAs using the 2nd edition of the AAP

HBB training curriculum for 2 days. On Day 1 of the training, all SBAs received pre-test knowledge and skills assessments in the order of MCQs, BMV, OSCE-A and OSCE-B, respectively. The pre-test was followed by integrated lectures and demonstrations on neonatal resuscitation skills. The topics covered during the training were: 1) the current global status of newborn health and the burden of neonatal morbidity and mortality, 2) birth preparedness in the labour suit, and 3) care of the healthy, sick and very sick newborn who require resuscitation and/or referral care. Question and answer sessions followed the lectures. The SBAs were then divided into three groups of 6–8 for further practical demonstrations and group practice of birth preparedness, ventilation skills, care of both healthy and sick newborn. A total of 6 h (3 h each day) was allowed for skills practice. Each group spent 2 h in each of the three skills sessions. During the different practical sessions, time was given for group practice in threes (a birth attendant, a mother and an assistant). The participants could ask the trainers and PI questions and clarifications on some difficult practical skills techniques. On the second day of the training, after all the SBAs were satisfied with the acquired resuscitation skills techniques, a post-test assessment was given in a similar way as the pre-test. Ongoing training was assessed at the end of each day using the Kirkpatrick training assessment tool to improve the quality of training and maximize learning [17].

### Intervention arm (standard HBB training and video-debriefing)

In addition to the standard HBB training, the intervention arm had their HBB simulation sessions video-recorded and used for debriefing. Participants were divided into two groups. One group remained in the video-debriefing session, while the other went for practical skills sessions as described in the standard HBB training alone. During debriefing, participants also worked in teams of threes (a birth attendant, a mother and an assistant). Prior to the debriefing, the participants were asked to set learning objectives at the beginning of each practical session using the SHARP (Set learning objectives, How it went, Address concerns, Review learning points, Plan ahead) debriefing tool [18]. At the end of each practice session, SBAs were asked how the session had gone and concerns arising from the practice were addressed. In addition, the learning objectives were reviewed, and the participants planned for improved performance. This was followed by viewing of the video recording by the group, with learning points and feedback being given by the participants in the simulation scenario, followed by the rest of the group members and the facilitator. After watching the video, the next team had their practice sessions. During each session, the facilitator read the case scenarios aloud. The team simulated this while being videotaped. This was done until every participant had had his/her turn to be a birth attendant. The objective assessment of debriefing (OSAD) tool was used to guide the facilitators during debriefing sessions [18].

Debriefing was done in a separate room from the HBB skills training rooms with participants and two debriefing leaders/facilitators in attendance. As in the control arm, all the participants in the intervention group were encouraged to practice while asking the facilitators questions and seeking clarification. Finally, post-training knowledge and skills assessment were given to the SBAs in the same way as in the control arm.

### Knowledge and skills assessment

Knowledge and skills attainment were defined as the percentage scores in knowledge and skills tests in the immediate post-training period. Skills assessments were done using validated HBB program tools (BMV, OSCE-A and OSCE-B checklists] for assessing neonatal resuscitation skills among SBAs using NeoNatalie manikin [5]. Knowledge was assessed using the standardised HBB MCQs. Assessments were done pre- and post-intervention, and during subsequent longitudinal follow-up at 1, 3 and 6 months. The skills scores were obtained by taking the means scores for BMV, OSCE-A and OSCE-B. Scores were presented in percentages and analysed as continuous variables.

### Outcome variables

The two outcomes measured were 1) knowledge and skills attainment in the immediate post-training period, and 2) knowledge and skills retention over a 6-month follow-up period.

### Independent variables (covariates)

Data were collected on the socio-demographic characteristics of SBAs (age, sex, educational qualifications and occupation), health unit type, number of deliveries at the health unit, HBB training experience, number of HBB training sessions attended and duration since last training, number of years spent in services, monthly number of neonatal resuscitations conducted prior to training, routine newborn resuscitation practices, and routine delivery care in the past 6 months. The occupation of the health workers was categorised as nurses/midwives, and clinical officers/doctors. Qualification was defined as the highest attained level of education: certificate, diploma, bachelor's degree, master's degree, and categorised as certificate, diploma or degree. HBB training experience was recorded as 'yes' if the person had ever attended at least one training. The duration since last training was recorded in months. Routine delivery and resuscitation practices were recoded as 'yes' if one provided delivery and neonatal resuscitation care at one's facilities on a regular basis or daily. The number of resuscitations per facility was counted from the birth registers and recorded as the number of babies resuscitated which was subsequently categorized as none, one or more. Each health worker was also asked to record the number of babies he/she had resuscitated in the previous month prior to the training. The number of deliveries was physically counted as the total number delivered per facility and health workers were also asked to record the average monthly number of deliveries attended and these were categorized as none, 1 to 9 and 10 or more.

### Quality control

Research assistants were trained, and the instruments pre-tested. The HBB trainers were nationally trained facilitators. The PI and research assistants were trained in neonatal resuscitation, assessment methods and debriefing by a master trainer from Sachs' Children and Youth Hospital, Stockholm, Sweden. Both internal and external validity, and reliability of the OSCE scores, were checked by the PI who participated in a few of the skills sessions while making independent observations.

### Data management and analysis

The Data were collected using standardized HBB knowledge (MCQ) and skills (BMV and OSCE-A & B) assessment tools. The data were entered using EPI Data 3.1 (EpiData Association; Enghavevej 34, DK5230 Odense M, Denmark) and exported to STATA Version 14 (StataCorp; College Station, TX, USA) for analysis.

Intention to treat analysis was done. At bivariable analysis, baseline categorical variables were summarized into proportions and presented in a table. Chi-squared tests were in bivariable analysis to screen for significant differences in baseline SBAs' sociodemographic and HF characteristics between intervention and control arms. Continuous variables were summarized as means with standard error. The mean differences between the two arms (intervention and control) were compared using two sample t-tests and the results presented in a table. The years in service and monthly number of resuscitations conducted which had *P*-value <0.10 at baseline bivariable analysis were included in the multilevel mixed effects linear regression model, in order to control for differences in baseline characteristics, clustering and repeated measurements from the same SBAs over time. Stratified analysis and adjustment in multivariable analysis for confounding were carried out. A factor was deemed confounding if 1) the crude and adjusted mean difference in scores deferred by ≥10%, and/or 2) the crude mean difference was outside the strata-specific mean difference ranges or known apriori (sex, age, and prior HBB training). The fixed and random effects were intervention and health facility clusters, respectively. The statistical significance level was set at a *P-value* < 0.05.

### Ethics

Ethical clearance was obtained from the Makerere University School of Medicine Research and Ethics Committee (SOMREC), reference number 2015–085, and the Uganda National Council of Science and Technology (UNCST), reference number HS 2478, the Ministry of Health through Lira District Health Office and health facility administrations. Clearance was also sought from the Norwegian Research Council. Assessment was done by the Norwegian Regional Committee for Medical and Health Research Ethics (REK Vest). The study was found to be outside their jurisdiction and hence qualified for exemption (2018/58/REK Vest). The study was registered at ClinicalTrials.gov (NCT03703622). Written informed consent was obtained from all the trial SBAs. Informed consent was also obtained from the participants before the video-recording. SBAs were not at risk, since we used simulation-based clinical case scenarios. For fairness of participation, we included SBAs from both public and private delivery facilities and from all HFs providing delivery and newborn care. Training frontline service providers (SBAs) ensured the provision of quality delivery and newborn care to reduce neonatal mortality in the region. This paper was prepared in accordance with CONSORT guidelines [19,20].

## Results

### Trial profile

The trial profile is presented in the CONSORT flow chart (Figure 1). A total of 26 HFs (clusters) were randomised into intervention or video-debriefing plus standard HBB training or control (standard HBB training only) in a ratio of 1:1 (Figure 1). Ninety-six SBAs were identified for training. After excluding seven who did not report for training and three who were providing neither delivery nor newborn care, 86 remained in the final sample. All the 26 clusters had SBAs trained and followed up for 6 months. The control arm witnessed a higher loss to follow-up throughout the study period. Follow-up at 6 months was about 95% (82/86).

### Characteristics of trial participants

The baseline characteristics were similar between groups except for the SBAs' years spent in services ($P = 0.04$) and the monthly number of resuscitations

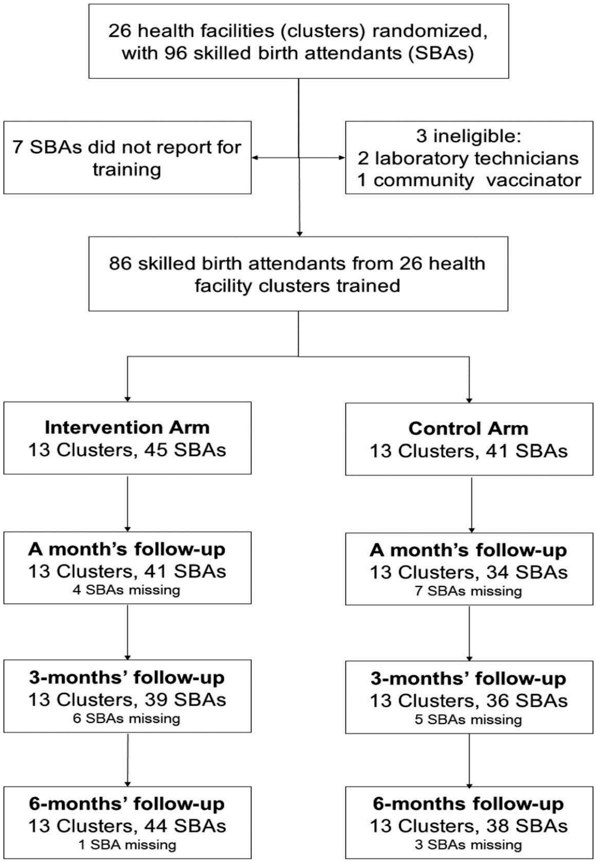


**Figure 1.** CONSORT flow chart trial participants.

conducted. Most of the SBAs (80%) had no prior HBB training before our intervention. Approximately 69% of the participants were from public (government) HFs and the majority of SBAs (84%) were from lower HFs (HCIIs and IIIs). Details are given in Table 1.

## Effects of video-debriefing on skills attainment and retention up to 6-months post-training

### *Knowledge and skills attainment*

Adding video-debriefing to standard HBB training had a significant effect on skills and the combined knowledge and skills (competence) attainment in the immediate post-training period after adjusting for baseline characteristics. Details are summarized in Table 2.

### *Knowledge and skills retention*

Adding video-debriefing to standard HBB training had significant effects on both skills and competence (knowledge and skills) retention over the 6-month period after controlling for differences in baseline characteristics (confounding) and clustering. SBAs who resuscitated at least one baby per month and those who had more than 5 years in service had less retention of neonatal resuscitation competence during the 6-month follow-up period. The summaries of mean differences and respective 95% CI of mean differences are presented in Table 3.

When we adjusted for SBAs' age, sex, monthly number of resuscitations, prior HBB training experience, and clustering instead of years in service at 6 months, the intervention effect on knowledge and skills mean difference remained statistically significant (adjusted mean difference: 3.76; 95% CI: 0.81–6.70). Details of analyses for confounding in Appendix.

## Trends in knowledge and skills mean scores between intervention arms over time

The overall knowledge and skills mean scores in both intervention and control arms improved in the immediate post-training period. In the follow-up period, the video-debriefing arm scored higher marks

**Table 1.** Sociodemographic characteristics of the trial participants.

| Characteristics | All n (%) N = 86 | Intervention n (%) N = 45 | Control n (%) N = 41 | *P* value |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 13(15.1) | 9(20.0) | 4(9.8) | 0.22 |
| Female | 73(84.9) | 36(80.0) | 37(90.2) | |
| **Qualification** | | | | |
| Degree/Diploma | 32(37.2) | 17(77.8) | 15(36.6) | 0.91 |
| Certificate | 54(62.8) | 28(62.2) | 26(63.4) | |
| **Profession** | | | | |
| Midwife/Nurse | 77(89.5) | 42(93.3) | 35(85.4) | 0.17 |
| Doctor/Clinical Officer | 9(10.47) | 3(6.7) | 6(14.6) | |
| **No. of Years in service** | | | | |
| ≤5 | 43(52.4) | 18(40) | 25(61.0) | |
| 6–15 | 26(30.2) | 15(33.3) | 11(26.8) | 0.27 |
| 15 | 17(19.8) | 12(26.7) | 5(12.2) | 0.04* |
| **Prior HBB trained** | | | | |
| Yes | 17(19.8) | 9(20.0) | 8(19.5) | 0.96 |
| No | 69(80.2) | 36(80.0) | 33(80.5) | |
| **Duration since last training** | | | | |
| ≤12 months | 9(52.9) | 4(44.4) | 5(62.5) | |
| >12 months | 8(47.1) | 5(55.6) | 3(37.5) | 0.37 |
| Not trained | 69(80.2) | 36(80.0) | 33(80.5) | 0.62 |
| **Number of HBB trainings** | | | | |
| once | 12(14.0) | 7(15.6) | 5(12.2) | |
| 2 or more | 5(5.8) | 2(44.4) | 3(7.3) | 0.54 |
| None | 69(80.2) | 36(80.0) | 33(80.5) | 0.74 |
| **Health Facility type** | | | | |
| Public | 59(68.6) | 39(86.7) | 20(48.8) | 0.12 |
| Private | 27(31.4) | 6(13.3) | 21(51.2) | |
| **Health Facility level** | | | | |
| Health Centre IV–V | 14(16.3) | 9(20.0 | 5(12.2) | 0.66 |
| Health Centre II–III | 72(83.7) | 36(80.0) | 36(87.8) | |
| **Routinely conducts delivery** | | | | |
| Yes | 71(82.3) | 38(84.4) | 33(80.5) | 0.66 |
| No | 15(17.4) | 7(15.6) | 8(19.5) | |
| **Monthly no. of deliveries** | | | | |
| ≥10 | 15(20.0) | 6(15.4) | 9(25.0) | |
| <10 | 60(69.8) | 33(73.3) | 37(65.9) | 0.39 |
| None | 11(12.8) | 6(23.3) | 5(12.2) | 0.49 |
| **Routinely resuscitates babies** | | | | |
| Yes | 63(75.0) | 36(80.0) | 27(69.2) | 0.27 |
| No | 21(25.0) | 9(20.0) | 12(30.8) | |
| **Monthly no. of resuscitations** | | | | |
| >1 | 19(22.1) | 7(15.6) | 12(29.3) | |
| 1 | 55(64.0) | 33(73.3) | 22(53.7) | 0.09 |
| None | 12(14.0 | 5(11.1) | 7(17.1) | 0.81 |

*p < 0.05 indicates significant baseline difference between intervention and control arms.

throughout. There was a marked difference in knowledge and skills scores with means scores for knowledge being significantly higher than the overall and individual skills components. It is important to note that, at baseline, all SBAs scored higher in knowledge than skills. The summaries of trends are presented in Figure 2; the P-value < 0.05 showed significant differences of means scores between intervention and control arms throughout the assessment.

When analysis was done at different time points as in Table 2, significant findings following adjustment for the differences in baseline characteristics, showed higher scores in intervention groups for bag and mask ventilation in the immediate post-test period. Similar observation was also seen for skills and the overall competence at the immediate post-test period and at 6 months. In Table 3, the overall mean scores were higher among the intervention group than those in control group over the 6-month period. What this means is that when scores are compared at different time points, the intervention effect is minimal on both competence and knowledge scores. However, pooling the scores over 6 months, a statistically significant difference exists between intervention and control arms with knowledge, skills and competence being higher in the video-debriefing arm than in the control arm. An analysis of variance (ANOVA) and a generalized estimation equation (GEE) models for the pooled analysis also yielded comparable results.

## Discussion

Our study showed that SBAs in the intervention arm were more likely to attain and retain neonatal resuscitation knowledge and skills than those in the control arm in the immediate post-training period and over a 6-month period. SBAs who routinely resuscitated at least one or more neonates per month and those who had spent more than 5 years in service exhibited reduced neonatal resuscitation competence

**Table 2.** Bivariable and multivariable analysis for effect of video-debriefing on knowledge and skills scores at different time points.

| | Intervention Mean (SE) | Control Mean (SE) | (Intervention – Control) Mean diff. (95% CI) | Adjusted[a] Mean diff (95% CI) | *P* value |
|---|---|---|---|---|---|
| Knowledge | | | | | |
| Pretest | 81.35(1.98) | 78.04(2.19) | 3.31(−2.54–9.16) | 1 | |
| Post test | 91.35(1.43) | 89.16(2.66) | 2.20(−3.60–7.99) | 3.96(−1.60–9.52) | 0.162 |
| 1 month | 87.88(1.54) | 86.71(1.56) | 1.17(−3.23–5.57) | 2.33(−2.07–6.73) | 0.300 |
| 3 months | 91.48(1.061) | 91.93(1.16) | 0.45(−3.60–2.69) | 0.65(−2.36–3.66) | 0.673 |
| 6 months | 91.25(1.47) | 90.19(1.56) | 1.06(−3.23–5.34) | 2.02(−2.02–6.01) | 0.326 |
| Bag Mask Ventilation | | | | | |
| Pretest | 39.05(3.38) | 40.50(4.09) | −1.45(−11.94–9.04) | 1 | |
| Post test | 94.99(1.10) | 85.88(3.55) | 9.12(2.13–16.10)* | 10.50(0.65–17.35) | 0.003* |
| 1 month | 95.12(1.57) | 92.69(1.96) | 2.42(−2.5 4–7.36) | 1.72(−3.27–6.72) | 0.499 |
| 3 months | 96.00(0.94) | 94.12(1.29) | 1.87(−1.27–5.02) | 2.17(−1.17–5.53) | 0.203 |
| 6 months | 95.25(1.07) | 91.36(2.03) | 3.89(−0.54–8.32) | 4.04(−1.08–9.16) | 0.122 |
| OSCE-A | | | | | |
| Pretest | 56.33(2.98) | 48.81(3.06) | 7.53(−0.99–16.04) | 1 | |
| Post test | 83.26(1.86) | 82.05(2.81) | 1.21(−5.33–7.74) | 2.61(−3.67–8.88) | 0.416 |
| 1 month | 83.40(1.89) | 83.06(2.41) | 0.34(−5.69–6.37) | 1.85(−3.85–7.56) | 0.524 |
| 3 months | 93.03(1.42) | 90.49(1.92) | 2.53(−2.16–7.23) | 2.66(−1.96–7.27) | 0.259 |
| 6 months | 92.59(1.56) | 89.48(1.68) | 3.11(−7.67–1.45) | 4.33(−0.12–8.78) | 0.057 |
| OSCE-B | | | | | |
| Pretest | 37.45(2.15) | 41.58(2.54) | −4.13(−10.72–2.46) | 1 | |
| Post test | 95.50(0.77) | 92.19(2.52) | 3.31(−1.64–8.26) | 4.30(−0.58–9.17) | 0.084 |
| 1 month | 90.21(0.73) | 89.66(1.45) | 0.55(−2.53–3.63) | 0.31(−2.66–3.27) | 0.838 |
| 3 months | 92.68(1.19) | 90.20(0.98) | 2.48(−0.65–5.60) | 3.56(−0.01–7.14) | 0.051 |
| 6 months | 92.99(1.01) | 90.58(1.12) | 2.41(−0.58–5.41) | 2.76(−0.41–5.94) | 0.087 |
| Skills | | | | | |
| Pretest | 44.28(2.16) | 42.77(2.71) | 1.50(−5.32–8.32) | 1 | |
| Post test | 91.25(0.90) | 86.70(2.59) | 4.55(−0.61–9.70) | 5.80(0.82–10.78) | 0.023* |
| 1 month | 89.57(1.05) | 88.47(1.55) | 1.10(−2.52–4.72) | 1.09(−2.47–4.65) | 0.549 |
| 3 months | 93.85(0.90) | 91.60(1.09) | 2.25(−0.55–5.04) | 2.75(−0.49–6.00) | 0.097 |
| 6 months | 93.65(1.00) | 90.52(1.40) | 3.13(−0.25–6.50) | 3.75(0.19–7.31) | 0.039* |
| Knowledge & skills | | | | | |
| Pretest | 53.55(1.89) | 52.23(2.30) | 1.32(−4.61–7.24) | 1 | |
| Post test | 91.28(0.92) | 87.32(2.56) | 3.96(−1.51–9.42) | 5.34(0.40–10.28) | 0.034* |
| 1 month | 89.15(1.01) | 88.03(1.25) | 1.12(−2.09–4.33) | 1.39(−1.72–4.50) | 0.381 |
| 3 months | 93.09(0.76) | 91.69(0.93) | 1.41(−0.99–3.81) | 1.97(−0.65–4.59) | 0.140 |
| 6 months | 93.07(0.98) | 90.45(1.26) | 2.62(−0.55–5.80) | 3.34(0.14–6.54) | 0.041* |

*$p < 0.05$, SE: Standard Error, diff.: difference. OSCE: Objective structured clinical examinations A & B, [a]Adjusted for years in service, number of resuscitations and clustering. Intervention only explains the BMV post-test result.

**Table 3.** Bivariable and multivariable mixed effects linear model for knowledge and skills retention by intervention over 6 months.

| | Intervention (Video-debriefing) Mean (SE) | Control Mean (SE) | Crude (Intervention – Control) Mean diff. (95% CI) | Adjusted[a] Mean diff. (95% CI) | *P* value |
|---|---|---|---|---|---|
| Knowledge | 88.67(0.73) | 87.01(0.94) | 1.65(−0.69–3.99) | 2.67(1.44–3.90) | <0.001* |
| Bag Mask Ventilation | 83.59(1.77) | 80.02(1.99) | 3.58(−1.66–8.82) | 3.70(−0.27–7.66) | 0.068 |
| OSCE-A | 81.37(1.30) | 78.10(1.59) | 3.27(−0.77–7.32) | 4.05(2.02–6.07) | <0.001* |
| OSCE-B | 81.35(1.64) | 79.98(1.71) | 1.37(−3.30–6.03) | 1.42(−1.54–4.37) | 0.347 |
| Skills | 82.18(1.45) | 79.46(1.66) | 2.72(−1.62–7.04) | 3.17(1.45–4.89) | <0.001* |
| Knowledge & skills | 83.93(1.17) | 81.36(1.38) | 2.57(−0.98–6.13) | 2.97(1.52–4.41) | <0.001* |

*P-Value < 0.05. SE: Standard Error. mean diff.: mean difference. OSCE: Objective structured clinical examination A & B, [a]Adjusted for years in service, routine resuscitation practices, clustering and assessment time interval.

retention during the follow-up period compared to their counterparts.

Several studies worldwide have shown that neonatal resuscitation knowledge and skills decline with time post-training, with skills showing an even faster rate of deterioration than what happens to knowledge [7,9,11,12]. Therefore, HBB training alone does not guarantee skills retention several months post-training. Our findings are in agreement with numerous other studies that have shown that low-cost interventions, such as daily manikin practice, regular review meetings and clinical case reviews improve health workers' performance, including retention of neonatal resuscitation skills [14,21,22]. The similarity of these studies with our findings could be due to repeated assessments at regular intervals which simulate quality improvement cycles reported by other studies. However, most of these studies had methodological limitations in assessing skills retention at individual levels without assessing the effect of clustering across health facilities. For example, a multicentre study in hospitals in Kenya and Nepal, reported that a combination of quality improvement cycle interventions improved neonatal resuscitation skills retention among SBAs [21]. The study relied on self-evaluation checklists filled-in by individual SBAs after every delivery and it is not clear if there were

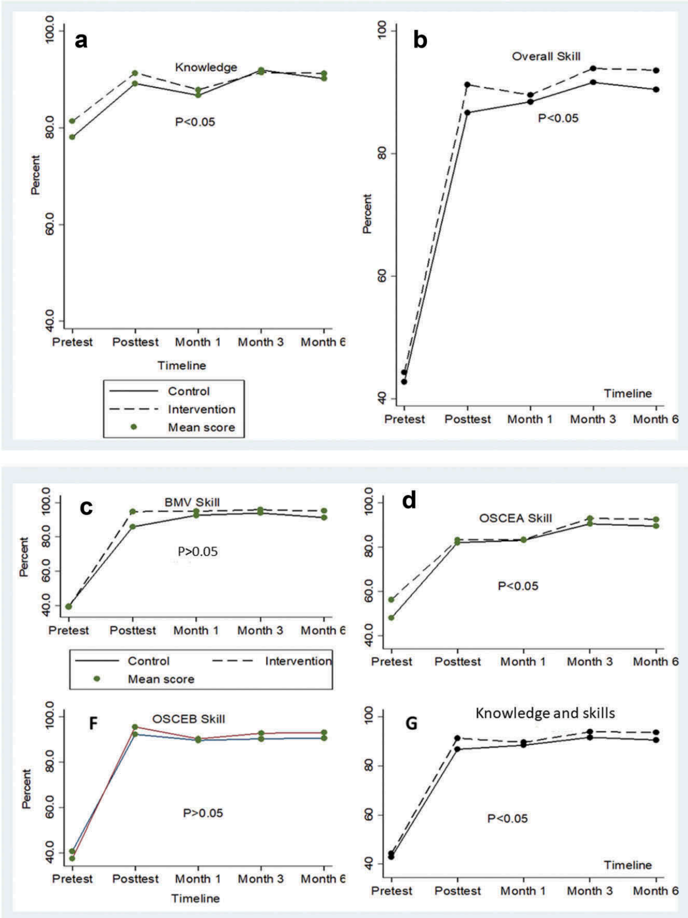


**Figure 2.** Knowledge and skills mean scores trends over 6 months.

The P-value < 0.05, for adjusted measurements over 6 months, signifies significant differences in mean scores between intervention and control groups.

discrepancies between what was reported and what was done by the SBAs. Furthermore, the presence of surveillance officers during quality improvement cycle meetings might also have affected the SBAs behaviour, which in turn could have introduced the Hawthorne effect (observer bias) in the reported results [21].

On the other hand, the skills retention seen in our study could have been influenced by frequent assessments at close intervals that could have pressured the health workers into revising prior to each assessment, as they were given both wall-charts and participant manuals for use in their respective facilities. A study in Honduras showed that frequent OSCE skills practice among both clinic- and hospital-based staff improved skills retention after 6-month post-training [22,23]. In the same study, it was also observed that skills declined sharply at 1-month post-training. Similarly, we found a slight decline in the overall knowledge and skills scores at 1-month post-training, with the intervention arm maintaining higher scores than the control arm throughout the follow-up period. There seemed to be a dose-response effect on the measures with each assessment period. Our study findings may also add to the list of intervention combinations to improve learning and skills retention among frontline maternal newborn healthcare workers over time. Consequently, this may improve neonatal outcomes as we aim for the 2030 SDG 3 regarding the reduction of neonatal mortality to <12 per 1,000 live births by that year.

Senior SBAs with more than 5 years in service demonstrated inferior knowledge and skills retention. A possible explanation could be that the older or senior SBAs felt that they had the experience and hence were slow at taking up new changes in newborn care practices. A study by Bang Akash and colleagues (2016) reported low skills retention among senior physicians who reported being *'too* *busy to practice neonatal resuscitation skills despite the provision of equipment in their facilities for daily practice'* [23]. This may, to some extent, explain our findings. We, however, did not conduct a qualitative study to ascertain the reasons for the low knowledge retention among senior SBAs in our study.

Lastly, SBAs who conducted routine neonatal resuscitation also demonstrated less knowledge and skills retention at 6 months. This finding contradicts a multicentre study from Nepal and Kenya which demonstrated a dose-response effect of refresher training and regular manikin practice on knowledge and skills retention [23]. This might be due to a perceived large workload and lack of time to read and refresh neonatal resuscitation knowledge.

### Limitations

The effect of frequent examinations of health workers could have led to improved performance and retention of neonatal resuscitation skills during the follow-up period. However, if this were the case, there would be no difference in retention between the arms. Despite the latter observation, the difference between arms remains significant. The strength of our study lies in it being a cluster-randomized trial with blinding of the assessors.

In order to minimize bias, there was explicit case definition of outcome measurements (knowledge and skills scores). Furthermore, correct addresses and telephone contacts for each participant were obtained to ensure minimal loss to follow-up. Data-cleaning was done to prevent misclassification. The calculated sample-size for individual randomization was 106, but we achieved only 86 participants in this study. This was overcome by cluster-randomization at the facility level, and all the calculated sample size of 26 clusters was followed-up for 6 months. We adjusted for differences in baseline characteristics, and clustering in the final analysis and there was very little intra-cluster variation. Studies on the validity of OSCE tool for assessment of resuscitation skills have reported fair to moderate agreement and this could have affected our scores between arms [5]. We overcame this by training our research assistants in scoring the SBAs. The interrater reliability was moderate to substantial with a kappa of 0.604 for overall skills scores.

## Conclusion

We have demonstrated that adding video-debriefing to HBB training had an effect on the overall skills and competence (combined knowledge and skills) attainment in the immediate post-training period and retention over a period of 6 months in an analysis carried out in Northern Uganda. The factors that reduced competence attainment and retention were a monthly number of resuscitations of one or more babies and years spent in service (notably more than 5 years).

### Recommendation

Debriefing is a cornerstone for simulation-based learning. If adding video-debriefing to the current standard HBB training curricula is to be justified in our context, more research is needed. A mixed method study on a bigger population should be embarked upon to assess the effectiveness of adding video-debriefing to standard HBB neonatal resuscitation training on the competence of frontline SBAs. This research should also incorporate qualitative and cost-benefit analyses. This will justify the scale up of video-debriefing for HBB in this context.

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## Author contributions

BO conceived the original study, developed the proposal, planned and executed the study, analysed and wrote the manuscript. TT, JKT, VN, & GN supervised the entire study from inception of the ideas to writing the manuscript. VA and NP participated in the training and assessment of the SBAs. In addition, VA actively participated in follow-up and manuscript drafting. DM actively participated in manuscript drafting. All authors approved the final manuscript.

## Disclosure statement

We declare that there was no potential conflict of interest.

## Ethics and consent

Ethics approval was obtained from Makerere University School of Medicine Research and Ethics Committee (SOMREC), reference number 2015-085, Uganda National Council of Science and Technology (UNCST), reference number HS 2478, the Norwegian Research Council through the Norwegian Regional Committee for Medical and Health Research Ethics (REK Vest). The study was found to be outside their jurisdiction and hence qualified for exemption (reference number 2018/58/REK Vest). This study was registered at ClinicalTrials.gov (NCT03703622). Lastly, written informed consent was obtained from all trial participants.

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## Paper context

Neonatal mortality reduction has been modest despite mass HBB training in low-resource settings. Prior to this study, it was unknown if video-debriefing would enhance SBAs' HBB competence in low-resource settings. However, this study revealed that adding video-debriefing to standard HBB training had some effect on competence retention over 6-month post-training compared to the usual practice. We recommend more research incorporating qualitative and cost-benefit analyses to prove its effectiveness and scalability.

## Availability of data and materials

Data will be available from the PI on reasonable request.

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# Appendix

**Table A1.** Sub group analysis of confounding factors for intervention in the immediate Post-training Bag Mask Ventilation and six-month knowledge and skills scores.

| | Sub group BMV mean difference immediate at 6 months | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Treatment arms mean difference | | Mean difference between each factor level (Yes-No or 1–0) | | | | Intervention adjusted for @ factor | | | |
| Factors (SBA) | Intervention | Control | Crude | P value | Adjusted | P value | Crude | Adjusted | % change | Confounder or Effect Modifier |
| Sex | 3.75(1.95–5.54) | 3.15(−11.43–17.73) | 5.08(−0.34–10.50) | 0.066 | 3.54(−1.24–8.31) | 0.147 | 9.18 | 8.86 | −3.5 | |
| Age | 0.030(−0.19–0.25) | −0.58(−1.43–0.27) | −0.16(−0.54–0.21) | 0.398 | −0.27(−0.70–0.16) | 0.212 | 9.18 | 9.99 | 8.8 | |
| Qualif2 | −0.92(−5.27–3.42) | −5.27(−19.58–9.04) | −2.75(−10.07–4.56) | 0.461 | −3.06(−10.33–4.21) | 0.409 | 9.18 | 9.11 | −0.8 | |
| Profess2 | −3.21(−7.07–0.65) | −5.06(−17.15–7.02) | −3.14(−10.87–4.60) | 0.427 | −4.23(−11.86–3.41) | 0.278 | 9.18 | 9.59 | 4.5 | |
| Years in service ≤5 years | −0.41(−4.90–4.09) | 13.87(−0.13–27.87) | 3.81(−3.09–10.72) | 0.279 | 6.43(−0.95–13.81) | 0.088 | 9.18 | 10.50 | 14.4 | Yes |
| HBB trained | 2.17(−2.16–6.50) | 7.27(−5.94–20.48) | 4.34(−2.30–10.99) | 0.200 | 4.54(−2.05–11.13) | 0.177 | 9.18 | 9.22 | 0.4 | Yes |
| Resuscitates routinely (Yes) | 0.22(−2.54–2.97) | −4.65(−15.01–5.71) | −1.44(−6.35–3.47) | 0.567 | −1.89(−7.50–3.72) | 0.509 | 9.18 | 9.44 | 2.8 | |
| Routine Delivery (Yes) | 1.46(−0.75–3.68) | −6.64(−17.05–3.77) | −2.26(−7.47–2.95) | 0.395 | −1.92(−7.23–3.39) | 0.478 | 9.18 | 9.20 | 0.2 | |
| # resuscitation (≥1 monthly) | 0.82(−2.03–3.68) | −4.65(−15.01–5.71) | −1.02(−6.08–4.03) | 0.691 | −1.66(−7.52–4.20) | 0.579 | 9.18 | 9.45 | 2.9 | |
| | ***Sub group competence mean difference immediate at 6 months*** | | | | | | | | | |
| ***Factors*** | ***Treatment arms mean difference*** | | ***Mean difference between each factor level (1–0)*** | | | | ***Intervention adjusted for @ factor*** | | | *Confounding or Effect Modification* |
| | ***Intervention*** | ***Control*** | ***Crude*** | ***P value*** | ***Adjusted*** | ***P value*** | ***Crude*** | ***Adjusted*** | ***% change*** | |
| Sex (Male) | −5.21(−13.16–2.75) | 4.38(1.14–7.62) | −1.41(−7.18–4.36) | 0.632 | −1.86(−7.99–4.28) | 0.553 | 2.48 | 2.68 | 8.1 | |
| Age in years | −0.01(−0.20–0.17) | −0.17(−0.49–0.14) | −0.06(−0.23–0.11) | 0.483 | −0.09(−0.71–6.28) | 0.343 | 2.48 | 2.79 | 12.5 | Yes |
| Qualification (Degree/Dipl) | −0.04(−5.80–5.72) | −1.15(−6.68–4.39) | −0.38(−4.35–3.59) | 0.850 | −0.60((−4.64–3.44)) | 0.770 | 2.48 | 2.51 | 1.2 | |
| Profession (MW/Nurse) Yes | 4.69(−12.63–22.02) | −6.14(−12.10,-0.19) | −1.88(−8.61–4.85) | 0.580 | −2.03(−9.35–5.30) | 0.588 | 2.48 | 2.60 | 4.8 | |
| Years in service ≤5 years | 2.53(−1.97–7.02) | 2.01(−3.56–7.58) | 1.79(−1.72–5.30) | 0.318 | 2.35(−1.16–5.86) | 0.189 | 2.48 | 3.00 | 21.0 | Yes |
| Prior HBB trained (Yes) | 2.70(−0.86–6.26) | 3.99(0.32–7.66) | 2.97(0.45–5.49) | 0.021 | 3.15(0.44–5.87) | 0.023 | 2.48 | 2.56 | 3.2 | |
| Resuscitates routinely (Yes) | −4.56(−7.56,-1.55) | −1.99(−6.10–2.12) | −3.12(−6.06,-0.18) | 0.037 | −3.17(−5.91,-0.42 | 0.024 | 2.48 | 2.73 | 25.0 | Yes |
| Routine Delivery (Yes) | −4.73(07.55,-1.92) | −7.50(−13.53,-1.46) | −5.74(−8.73,-2.75) | <0.001 | −5.70(−8.62,-2.77) | <0.001 | 2.48 | 2.53 | 5.0 | |
| # resuscitation (≥1 monthly) | −4.82(−7.85,-1.79) | −1.99(−6.10–2.12) | −3.14(−6.23,-0.06) | 0.046 | −3.22(−6.07,-0.37) | 0.027 | 2.48 | 2.80 | 32 | Yes |
| # Deliveries ≥10 monthly | 0.40(−3.98–4.79) | −0.33(−3.69–3.04) | −0.04(−2.87–2.79) | 0.977 | 0.03(−2.58–2.65) | 0.980 | 2.48 | 2.48 | 0.0 | |

Factors with more ≥10% difference between crude and adjusted mean difference between intervention arms was adjusted for in the multivariable mixed effects linear regression model in the immediate post-training period and at six months for bag mask ventilation competence respectively.

# Annex I

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*Article*

# Incidence and Risk Factors for Low Birthweight and Preterm Birth in Post-Conflict Northern Uganda: A Community-Based Cohort Study

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**Abstract:** Background: Annually, an estimated 20 million (13%) low-birthweight (LBW) and 15 million (11.1%) preterm infants are born worldwide. A paucity of data and reliance on hospital-based studies from low-income countries make it difficult to quantify the true burden of LBW and PB, the leading cause of neonatal and under-five mortality. We aimed to determine the incidence and risk factors for LBW and preterm birth in Lira district of Northern Uganda. Methods: This was a community-based cohort study, nested within a cluster-randomized trial, designed to study the effect of a combined intervention on facility-based births. In total, 1877 pregnant women were recruited into the trial and followed from 28 weeks of gestation until birth. Infants of 1556 of these women had their birthweight recorded and 1279 infants were assessed for preterm birth using a maturity rating, the New Ballard Scoring system. Low birthweight was defined as birthweight <2.5kg and preterm birth was defined as birth before 37 completed weeks of gestation. The risk factors for low birthweight and preterm birth were analysed using a multivariable generalized estimation equation for the Poisson family. Results: The incidence of LBW was 121/1556 or 7.3% (95% Confidence interval (CI): 5.4–9.6%). The incidence of preterm births was 53/1279 or 5.0% (95% CI: 3.2–7.7%). Risk factors for LBW were maternal age ≥35 years (adjusted Risk Ratio or aRR: 1.9, 95% CI: 1.1–3.4), history of a small newborn (aRR: 2.1, 95% CI: 1.2–3.7), and maternal malaria in pregnancy (aRR: 1.7, 95% CI: 1.01–2.9). Intermittent preventive treatment (IPT) for malaria, on the other hand, was associated with a reduced risk of LBW (aRR: 0.6, 95% CI: 0.4–0.8). Risk factors for preterm birth were maternal HIV infection (aRR: 2.8, 95% CI: 1.1–7.3), while maternal education for ≥7 years was associated with a reduced risk of preterm birth (aRR: 0.2, 95% CI: 0.1–0.98) in post-conflict northern Uganda. Conclusions: About 7.3% LBW and 5.0% PB infants were born in the community of post-conflict northern Uganda. Maternal malaria in pregnancy, history of small newborn and age ≥35 years increased the likelihood of LBW while IPT reduced it. Maternal HIV infection was associated with an increased risk of PB compared to HIV negative status. Maternal formal education of ≥7 years was associated with a reduced risk of PB compared to those with 0–6 years. Interventions to prevent LBW and PBs should include girl child education, and promote antenatal screening, prevention and treatment of malaria and HIV infections.

**Keywords:** preterm birth; low birthweight; risk factors; community-based; cohort study

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## 1. Background

Of the 140 million infants born worldwide in 2014, an estimated 20 million (13%) were born with low birthweight (<2.5 kg) [1]. Ninety percent (18/20 million) of LBW infants were born in low- and middle-income countries (LMICs) [2]. In sub-Saharan Africa, LBW prevalence varied from 7.0% to 18.0%, with the highest prevalence observed in malaria-based studies in Tanzania [3]. According to the Uganda Bureau of Statistics (UBOS) 2011, 10.4% of all live-born infants nationwide and 11.4% in the northern part of the country are LBW [4].

In 2010, an estimated 15 (uncertainty range 12–18) million preterm infants were born worldwide [5]. The global PB estimates ranges from 5% in Europe to 18% in some sub-Saharan African countries [5]. Sub-Saharan Africa and South Asia contribute 52%–60% of the global PB burden [5]. In Uganda, reports of the proportion of PBs range from 4.1% to 15% [5,6], In communities of post-conflict northern Uganda, however, its true burden is unknown.

Multiple maternal and foetal causes of LBW and/or PB (small birth size) have been described [7]. The age of the mother, either young (teenage 12–16 years) or old (≥35 years) has been linked to increased risk of small birth size [8,9]. Low maternal socio-economic and education status has been associated with small birth size [10–12]. Furthermore, maternal ill-health during pregnancy such as malaria and HIV infection, low body mass index (BMI) or low gestational weight gain, and hypertension have also been associated with small birth size [13,14]. A history of having given birth previously to a small infant has also been associated with LBW and/or PB recurrence in subsequent pregnancies [15–17]. Whereas some studies report increased risk of small birth size among women who do excessive physical work, a 2013 meta-analysis found little to no effect of the same on small birth sizes [18]. Foetal factors associated with LBW and PB include: congenital malformations, multiple foetuses, sex, and genetic factors [19,20].

In high-income countries, common causes of small birth size include provider-initiated caesarean section and assisted reproduction, [7] while in low-resource settings, it is related to maternal infections, low socio-economic status, malnutrition, and history of preterm birth or low birthweight. In post-conflict northern Uganda, however, the social disruption, lack of schooling and displacement caused by the 20 years of conflict may have modified the burden and some of the known risk factors for small birth size. Few studies exist to describe the burden of LBW and PB during the post-conflict period in northern Uganda [3].

To achieve the sustainable development goal (SDG) 3.2 target of neonatal mortality below 12 per 1000 live births by 2030, there is an urgent need to generate post-conflict context specific data on small newborns' (LBW and PB) health burden and associated modifiable risk factors. We, therefore, aimed to (1) estimate the incidence of and (2) determine risk factors for low birthweight and preterm birth in post-conflict northern Uganda.

## 2. Methods

This was a cohort study nested within the Survival Pluss cluster randomized trial. The Survival Pluss study assessed the effect of an integrated package consisting of (i) peer support by pregnancy buddies, (ii) provision of mama (birth) kits at household level (as opposed to health facility distribution) and (iii) mobile phone messaging on facility-based births. In the trial, pregnant women were enrolled at ≥28 weeks of gestation and followed up to delivery (ClinicalTrials.gov number NCT0260505369).

The study was conducted in Lira District, Northern Uganda from July 2017 to March 2019. Lira District had a population of about 400,000 people in 2010, dwelling in 13 sub-counties, a city and 751 villages. Lira district was chosen based on its being a post-conflict area with poor maternal and child health indicators, low proportion of health facility deliveries, high neonatal mortality, and limited data on LBW and PBs burden and associated risk factors [21]. The study sites were Aromo, Agweng, and Ogur sub-counties; also chosen because they had the poorest maternal and child health indicators [9]. Each sub-county had one health centre with maternity (health centre, HC III or HC IV), and two additional lower-level health centres without maternity (HC II). Two of the HC IIIs (Agweng and Aromo), however, were not conducting deliveries before the project inception.

A total of 1877 mothers were recruited into the trial at 28 weeks of gestation and followed up to birth. Of these, 1556 mother-infant dyads with birthweight (for LBW burden) and 1279 had both a gestational age estimate using the New Ballard Score (NBS) and birthweight (for PB burden). Only 4 persons conducted the NBS assessment, hence some infants had birthweight (from the clinic or study staff) but not gestational age estimate.

The primary outcomes were incidence of (1) low birthweight births and (2) preterm births. Independent or exposure variables were maternal and infant factors. Maternal socio-demographic (maternal age in completed years, years of formal education, paternal occupation, marital status, wealth index groups, intervention, and domestic water source) and clinical factors (parity, HIV serostatus, malaria in pregnancy, intermittent preventive treatment (IPT) for malaria in pregnancy, history of a small newborn, multiple pregnancy, and antenatal care (ANC) attendance and infant factor (sex), were analysed for association with LBW and PB.

A low birthweight (LBW) was defined as birthweight <2.5 kg at birth, while preterm birth (PB) was defined as being born after 28 weeks of gestation but before 37 completed weeks of gestation [22]. We calculated the incidence (risk) as the number events (LBW or PB) divided by total number of live births (population at risk), during the study period from July 2017 to March 2019, expressed as a percentage. Birthweight was measured using a digital floor scale with mother/child function (seca, Hamburg, Germany) and recorded to the nearest 2 decimal points in kilograms. Gestational age (GA) was estimated using the New Ballard Score (NBS), which employs both physical and neuromuscular maturation. The total physical maturation (PM) and neuromuscular maturation (NM), also known as maturity rating total scores (MRTS), was correlated with gestational age, recorded in completed weeks. The MRTS, ranging from −10 to 50, were then extrapolated to foetal age in weeks (20 to 44). Maternal age was recorded in completed years and categorised into three groups as 12–19, 20–34, and 35–49 years. Education was recorded in years of completed schooling and dichotomized as 0–6 and 7 or more years in school. Marital status was categorised as binary variable into 'married' or 'single/separated/divorced/widowed'. Wealth index quintiles were calculated using Gini index based on several key household assets and classified ranging from the 1 'poorest' to 5 'wealthiest' quintiles. This was further sub-grouped into three wealth groups as follows: the lower 40% (1st–2nd quintiles), the middle 40% (3rd–4th quintiles) and the upper 20% (5th quintile). Paternal occupation was categorized during analysis as farmer, employed or unemployed. Domestic water source was categorised as 'tap/borehole' or 'spring/well/river/ponds. A history of small newborn was ascertained if the answer was a 'yes' to the following statements: if the mother (i) mother was told by the skilled birth attendant that her infant was small at birth in the previous pregnancy based on birthweight measurement, or (ii) had history of a small infant at birth by her own assessment in prior pregnancy, or (iii) recalled the birthweight from the previous delivery which we used to categorize the infants as LBW or not, and (iv) reported that the infant was born before term in which case, we asked the mother the gestation age at birth and used it to categorise them into preterm birth (<7 months) or term (≥7 months of gestational age). Parity was the number of pregnancies the mother had before, and further re-categorised as 'prime gravida (first time mother)', '1–6′ and '7 or more' children. The presence of maternal illnesses during pregnancy such as malaria or HIV were recorded as ('yes' 'no', or 'unknown') based on antenatal test results. Antenatal care (ANC) attendance was recorded as 'yes' if the woman attended antenatal clinic at least once during the current pregnancy. Maternal malaria IPT in pregnancy was recorded as 'yes' if the mother received intermittent preventive treatment for malaria during pregnancy. Intervention was recorded as 'yes' if the mother received the Survival Pluss intervention package (mama kit, SMS, and peer buddies) during pregnancy. We analysed sub-samples of mother-infant pairs from the Survival Pluss cohort who had infants with birthweight (1556) or both birthweight and gestational age by NBS assessment (1279), respectively. We compared the included to the excluded sample and there was minimal difference in baseline socio-demographic characteristics between the analysed and excluded groups except for maternal age in the PB sample and health facility delivery and father's occupation in the LBW sample, (Table 1). The Survival Pluss study included and followed all pregnant women in the participating communities from 28 weeks of gestation, who had no intention of moving away from the study area within a year of enrolment and who had no psychiatric illness that could inhibit the informed consent process. We excluded infants whose parents declined newborn examinations, those who died at birth or who had severe congenital abnormalities (anencephaly and exomphalos) and those without birthweight (for LBW) and without birthweight and NBS (for PBs).

**Table 1.** Comparison of baseline characteristics between included and excluded study participants in the two analyses—low birthweight and preterm birth—in Northern Uganda.

| **Characteristics** | **Low Birthweight** | | | | **Preterm Birth** | | | |
|---|---|---|---|---|---|---|---|---|
| | **All N = 1877 n (%)** | **Analysed N = 1556 n (%)** | **Excluded N = 321 n (%)** | ***p* Value** | **All N = 1877 n (%)** | **Analysed N = 1279 n (%)** | **Excluded N = 598 n (%)** | ***p* Value** |
| Maternal characteristics | | | | | | | | |
| Maternal age | | | | | | | | |
| 12–19 years | 510 (27.2) | 415 (26.7) | 95 (29.6) | | 510 (27.2) | 330 (25.8) | 180 (30.1) | |
| 20–34 years | 1174 (62.5) | 982 (63.1) | 192 (59.8) | 0.325 | 1174 (62.5) | 815 (63.7) | 359 (60.0) | 0.017 |
| ≥35 years | 193 (10.3) | 159 (10.2) | 35 (10.6) | | 193 (10.3) | 134 (10.5) | 59 ( 9.9) | |
| Maternal education | | | | | | | | |
| 0–6 years | 1515 (80.7) | 1246 (80.1) | 269 (83.8) | | 1515 (80.7) | 1032 (80.7) | 483 (80.8) | |
| ≥7 years | 362 (19.3) | 310 (19.9) | 52 (16.2) | 0.117 | 362 (19.3) | 247 (19.3) | 115 (19.2) | 0.896 |
| Maternal vocational education | | | | | | | | |
| No | 1663 (88.6) | 1371 (88.1) | 292 (92.0) | | 1663 (88.6) | 1131 (88.4) | 532 (89.0) | |
| Yes | 214 (11.4) | 185 (11.9) | 29 ( 8.9) | 0.224 | 214 (11.4) | 148 (11.6) | 66 (11.0) | 0.700 |
| Marital status | | | | | | | | |
| Married | 1708 (91.0) | 1417 (91.1) | 291 (90.7) | 0.495 | 1708 (91.0) | 1166 (91.2) | 542 (90.6) | 0.557 |
| Single/separated/divorced/widow | 169 ( 9.0) | 139 ( 8.9) | 30 ( 9.3) | | 169 ( 9.0) | 113 (8.8) | 56 ( 9.4) | |
| Wealth index | | | | | | | | |
| Lower 40% | 837 (44.6) | 708 (45.5) | 129 (40.2) | | 837 (44.6) | 574 (44.9) | 263 (44.0) | |
| Middle 40% | 665 (35.4) | 547 (35.2) | 118 (36.8) | 0.329 | 665 (35.4) | 465 (36.4) | 200 (33.4) | 0.139 |
| Upper 20% | 375 (20.0) | 301 (19.3) | 74 (23.0) | | 375 (20.0) | 240 (18.8) | 135 (22.6) | |
| Father's occupation | | | | | | | | |
| Farmer | 1275 (67.9) | 1058 (68.0) | 217 (67.6) | | 1275 (67.9) | 883 (69.1) | 392 (65.5) | |
| Employed | 390 (20.8) | 348 (22.4) | 42 (13.1) | 0.022 | 390 (20.8) | 274 (21.4) | 116 (19.4) | 0.688 |
| Unemployed | 168 ( 9.0) | 150 ( 9.6) | 18 ( 5.6) | | 168 ( 9.0) | 122 ( 9.5) | 46 ( 7.7) | |
| Missing | 44 ( 2.3) | 0 ( 0.0) | 44 (13.7) | | 44 ( 2.3) | 0 ( 0.0) | 44 ( 7.4) | |
| Domestic water source | | | | | | | | |
| Tap/Borehole | 1188 (63.3) | 977 (62.8) | 211 (65.7) | 0.459 | 1188 (63.3) | 802 (62.7) | 386 (64.6) | 0.268 |
| Spring/river/well/stream/pond | 689 (36.7) | 579 (37.2) | 110 (34.3) | | 689 (36.7) | 477 (37.3) | 212 (35.4) | |
| Intervention | | | | | | | | |
| No | 855 (47.2) | 740 (47.6) | 145 (45.2) | | 885 (47.2) | 601 (47.0) | 284 (47.5) | |
| Yes | 992 (52.9) | 816 (52.4) | 176 (54.8) | 0.625 | 992 (52.8) | 678 (53.0) | 314 (52.5) | 0.956 |
| Facility Delivery | | | | | | | | |
| No | 644 (34.3) | 484(31.1) | 160 (49.8) | | 644 (34.3) | 397 (31.0) | 247 (41.3) | |
| Yes | 1233 (65.7) | 1072(68.9) | 161 (50.2) | 0.000 | 1233 (65.7) | 882 (67.0) | 351 (58.7) | 0.000 |
| Maternal clinical characteristics | | | | | | | | |
| History of small infant | | | | | | | | |
| No | 1131 (60.2) | 985 (63.3) | 146 (45.5) | | 1131 (60.3) | 964 (75.4) | 167 (30.2) | |
| Yes | 317 (16.9) | 218 (14.0) | 99 (30.8) | 0.000 | 317 (16.9) | 40 ( 3.1) | 277 (50.0) | 0.000 |
| Prime gravida | 429 (22.9) | 353 (22.7) | 76 (23.7) | | 429 (22.9) | 275 (21.5) | 154 (27.8) | |
| Parity | | | | | | | | |
| Prime gravida | 429 (22.9) | 353 (22.7) | 76 (23.7) | | 429 (22.9) | 275 (21.5) | 154 (25.7) | |
| 1–6 | 1257 (67.0) | 1043 (67.0) | 214 (66.8) | 0.857 | 1257 (67.0) | 872 (68.2) | 385 (64.4) | 0.025 |
| 7 or more | 191 (10.2) | 160 (10.3) | 31 ( 9.7) | | 191 (10.2) | 132 (10.3) | 59 ( 9.9) | |
| Maternal HIV infection | | | | | | | | |
| No | 1708 (91.0) | 1455 (93.5) | 253 (78.8) | | 1708 (91.0) | 1205 (94.2) | 503 (84.1) | |
| Yes | 83 ( 4.4) | 73 ( 4.7) | 10 ( 3.1) | 0.000 | 83 ( 4.4) | 61 ( 4.8) | 22 ( 6.7) | 0.000 |
| Unknown | 86 ( 4.6) | 28 ( 1.8) | 58 (18.1) | | 86 ( 4.6) | 13 ( 1.0) | 73 (12.2) | |
| Antenatal attendance | | | | | | | | |
| No | 395 (21.0) | 352 (22.6) | 43 (13.4) | | 395 (21.0) | 283 (22.1) | 112 (18.7) | |
| Yes | 1482 (79.0) | 1204 (77.4) | 278 (86.6) | 0.000 | 1482 (79.0) | 996 (77.9) | 486 (81.3) | 0.088 |
| IPT [a] for malaria in pregnancy | | | | | | | | |
| No | 764 (40.7) | 704 (45.2) | 60(18.7) | | 764 (40.7) | 695 (54.3) | 69 (11.5) | |
| Yes | 1113 (59.3) | 852 (54.8) | 261 (81.3) | 0.000 | 1113 (59.3) | 584 (45.7) | 529 (88.5) | 0.000 |
| Maternal malaria in pregnancy | | | | | | | | |
| No | 602 (32.1) | 502 (32.3) | 100 (31.2) | | 602 (32.1) | 272 (45.5) | 330 (25.8) | |
| Yes | 459 (24.4) | 388 (24.9) | 71 (22.1) | 0.245 | 459 (24.4) | 117 (19.6) | 342 (26.7) | 0.000 |
| Unknown | 816 (43.5) | 666 (42.8) | 150 (46.7) | | 816 (43.5) | 209 (35.0) | 607 (47.5) | |
| Infant sex | | | | | | | | |
| Female | 892 (47.5) | 757 (48.7) | 135 (42.0) | | 892 (47.5) | 620 (48.5) | 272 (45.5) | |
| Male | 943 (50.2) | 799 (51.3) | 144 (44.9) | 0.950 | 943 (50.2) | 659 (51.5) | 284 (47.5) | 0.816 |
| Missing | 42 ( 2.3) | 0 ( 0.0) | 42 (13.1) | | 42 (2.2) | 0 (0.0) | 42 (7.0) | |

N/n (%) frequency (percentage), [a] IPT = Intermittent preventive treatment for malaria.

### 2.1. Study Procedures

Prior to recruitment, research assistants were trained on the study protocol, weight measurement, and electronic data collection tool, the open data kit (ODK) software (https://opendatakit.org/ (accessed on 6 December 2017)), and the New Ballad Scoring system (NBS) for gestational age assessment. Pregnant mothers were identified by community recruiters who informed the study team. The research assistants were then dispatched to see the identified mothers. Those who met the inclusion criteria were consented and recruited. The enrolled pregnant women were followed up to birth and postnatally to two and seven days, for birthweight and administration of the NBS, respectively. The neonatal anthropometrics (birthweight) and NBS were done within two days and seven days for accurate determination of birthweight and gestation age, respectively. After birth, the same recruiters informed the study team who in turn visited the mother-infant dyads at birth for delivery questionnaire administration and anthropometric (birthweight, length, head, chest and abdominal circumferences) measurements. The weighing scales and length/height boards were calibrated before each field visit and before each measurement was taken. The weighing scales were checked for accuracy daily with known standard weights. Data was collected using standardized pre–coded questionnaires in ODK, and immediately sent to the server for safe custody by the data manager. Data cleaning and checking for completeness were done for quality control throughout the data collection process.

A total of four research nurses and midwives were trained on the NBS tool. The overall intra-rater (percentage agreement: 82.56%, kappa: 0.806, 95% CI: 0.788–0.823) and inter-rater (percentage agreement: 77.5%; kappa: 0.774, 95% CI: 0.613–0.936) reliability for the Ballard scoring tool were strong. The principal investigator (BO) worked with and supervised the research assistants on data collection and documentation.

### 2.2. Statistical Analysis

The data collected using ODK was sent to a server from where it was downloaded to Stata 14 (Stata Corp, College Station, TX, USA) for analysis. The incidence of LBW and PB were sex standardized and cluster adjusted and presented as the proportion of LBW and PBs to the total number of live births reported in percent (see Table 2 in Results Section. Descriptive statistics for categorical variables were summarized into proportions and the results presented in (see Tables 3 and 4, Results Section). Inferential statistics (the risk factors for LBW and PB), were analysed using bivariable and multivariable generalised estimation equation for the binary categorical outcome of LBW and PB (see Tables 3 and 4 in Results Section). Significant factors with $p$ value $\leq 0.05$ at bivariable analysis were taken into the multivariable generalized estimation equation model with a log link to Poisson family, adjusting for clustering and potential confounding. Known risk factors for LBW and PB such as infant sex, wealth index, and integrated intervention were also added into the final model. The crude and adjusted risk ratios were compared during the multivariable regression analysis. A difference of $\geq$10% between crude and adjusted risk ratios were considered confounding.

## 3. Results

### 3.1. Study Profile

Of the 1877 pregnant women recruited into Survival Pluss trial, 44 were lost to follow-up, 277 had missing birthweight and further 277 were not reached in time for gestational age estimation by NBS. Of those with birthweight, 7.8% (121/1556) were LBW and of those with gestational age estimate, 4.1% (53/1279) were assessed to be born preterm. Of the LBW infants with gestational age, 19% (20/105) were considered preterm while 37.7% (20/53) of preterm infants were low birthweight (Figure 1).

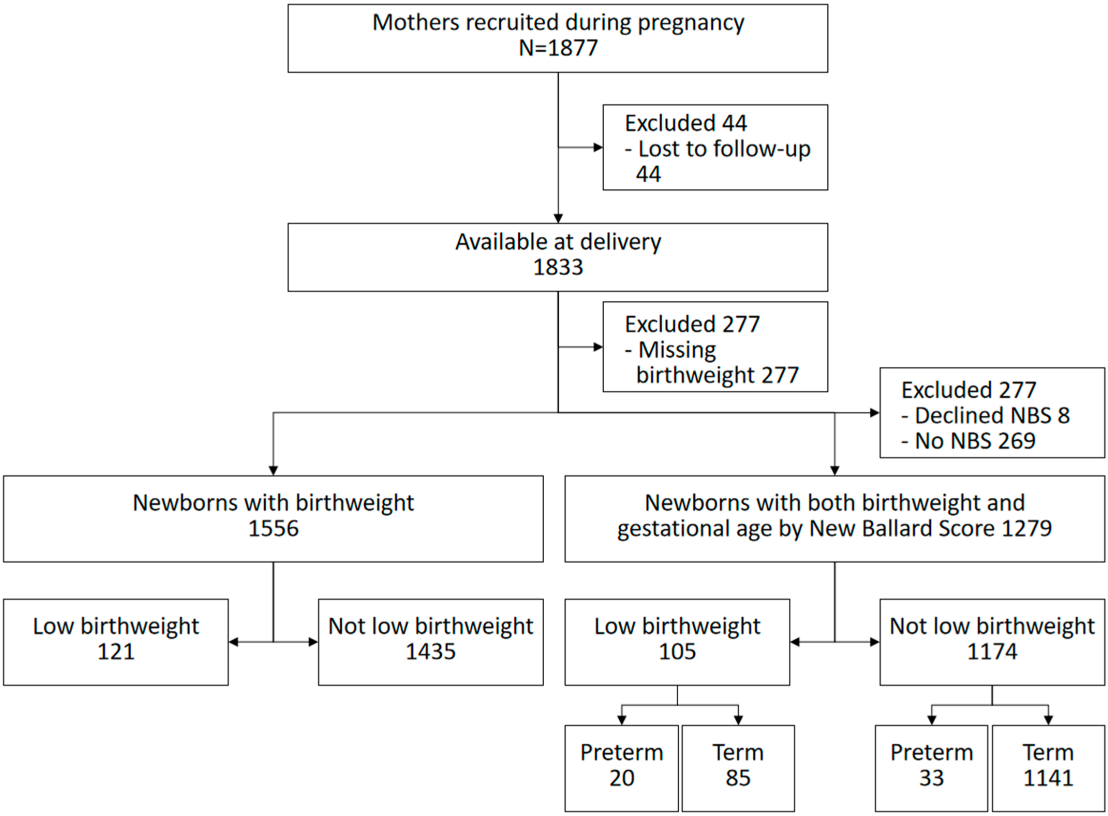


**Figure 1.** Study profile.

### *3.2. Baseline and Clinical Characteristics of Study Participants*

Of the 1556 mother-infant dyads, a quarter of the mothers were first time mothers (prime gravida), 22 (1.4%) were twins, and 90% were married. Most of the fathers were subsistence farmers. Most families used tap or borehole water for domestic consumption. Around 4.4% of the mothers were HIV seropositive, while up to 4.6% did not know their HIV status. Close to 16.9% of mothers had prior history of small newborn in the most recent (second last) delivery. The male to female ratio approximated 1:1, Table 1.

### *3.3. The Incidence of Low Birthweight and Preterm Birth*

#### 3.3.1. Low Birthweight

The number of low birthweight infants was 121/1556, 7.7%. The sex and cluster adjusted incidence of LBW in post-conflict northern Uganda was 7.3% (95% Confidence interval (CI): 5.4%–9.6%).

#### 3.3.2. Preterm Birth

The incidence of preterm births assessed by NBS was 53/1279 or 4.1%. The sex and cluster adjusted incidence of PB in post-conflict northern Uganda was 5.0% (95% CI: 3.2%–7.7%). The New Ballard Score being subjective, we analysed in a sensitivity analysis, the effect of potential systematic over–scoring of the maturity rating total score (MRTS) on the incidence of preterm birth (Table 2). The crude and the sex and cluster adjusted incidence of preterm birth is presented in case the infants were over–scored by 1, 2, 3, or 4 MRTS.

**Table 2.** Sensitivity analysis of the incidence of preterm birth based on the New Ballard among 1279 infants in Northern Uganda.

| | Crude Incidence of Preterm Birth (95% CI) | Cluster and Adjusted Incidence of Preterm Birth (95% CI) |
|---|---|---|
| Using the original New Ballard Score | 4.1% (3.0–5.8%) | 5.0% (3.2–7.7%) |
| Subtracting 1 score point from the New Ballard Score | 5.5% (4.4–6.9%) | 6.4% (4.4–9.2%) |
| Subtracting 2 score points from the New Ballard Score | 7.8% (6.5–9.6%) | 8.6% (6.1–12.2%) |
| Subtracting 3 score points from the New Ballard Score | 12.1% (10.4–14.0%) | 13.1% (10.0–16.9%) |
| Subtracting 4 score points from the New Ballard Score | 17.1% (15.2–19.3%) | 17.8% (14.6–21.4%) |

CI confidence interval.

### 3.4. Risk Factors for Low Birthweight and Preterm Birth

#### 3.4.1. Low Birthweight

The factors that were associated with increased risk of a low birthweight infants in our cohort were advanced maternal age (≥35 years), history of a small newborn in prior pregnancy, malaria infection, and unknown malaria status in pregnancy (Table 3). Infants born to mothers aged 35 or more years were two (adjusted RR 1.9 (95% CI: 1.1 –3.9) times more likely to be LBW compared to those born to mothers aged 20–34 years. A history of a small newborn in the second last pregnancy doubled the risk (aRR: 2.1, 95% CI: 1.2–3.4) of LBW compared to those without. A positive malaria test (aRR: 1.7, 95% CI: 1.01–2.9) or an unknown malaria status during pregnancy (aRR 1.9, 95% CI: 1.1–3.2) almost doubled the risk of LBW among the infants compared to those with known malaria negative tests. On the other hand, infants whose mothers received intermittent preventive treatment for malaria during pregnancy had a 40% (aRR 0.6, 95% CI: 0.4–0.8) reduced risk of being LBW compared to those who did not. The integrated intervention package had no effect on the LBW in this post conflict setting of northern Uganda. These and more details are summarized in Table 3. Similarly, other known risk factors for LBW such as poverty, maternal education, teenage motherhood, grand multi–parity, ANC attendance and HIV infection were not associated with an increased risk of LBW among mothers in the cohort.

**Table 3.** Bi- and multi-variable analysis of risk factors for low birthweight in northern Uganda.

| Characteristics | All N = 1556 n (%) | LBW N = 121 n (%) | Crude RR (95% CI) N = 1556 | *p* Value | Adjusted RR (95% CI) N = 1556 | *p* Value |
|---|---|---|---|---|---|---|
| Maternal characteristics | | | | | | |
| Maternal age | | | | | | |
| 12–19 years | 415 (26.7) | 40 (33.1) | 1.4 (1.0–2.0) | 0.048 | 1.3 (0.8–2.1) | 0.351 |
| 20–34 years | 982 (63.1) | 67 (55.4) | Ref | | | |
| ≥35 years | 159 (10.2) | 14 (11.6) | 1.3 (0.9–1.9) | 0.183 | 1.9 (1.1–3.4) | 0.021 |
| Maternal education | | | | | | |
| 0–6 years | 1246 (80.1) | 91 (75.2) | Ref | | | |
| ≥7 years | 310 (19.9) | 30 (24.8) | 1.3 (0.9–2.0) | 0.190 | 1.4 (0.9–2.3) | 0.102 |
| Maternal vocational education | | | | | | |
| No | 1371 (88.1) | 103 (85.1) | Ref | | | |
| Yes | 185 (11.9) | 18 (14.9) | 1.3 (0.8–2.1) | 0.297 | | |
| Marital status | | | | | | |
| Married | 1417 (91.1) | 110 (90.9) | 1.0 (0.5–1.8) | 0.951 | | |
| Single/separated/divorced/widowed | 139 (8.9) | 11 (9.1) | Ref | | | |
| Wealth index groups | | | | | | |
| Lower 40% | 708 (45.5) | 62 (51.2) | Ref | | | |
| Middle 40% | 547 (35.2) | 40 (33.1) | 0.8 (0.6–1.3) | 0.379 | 0.8 (0.6–1.3) | 0.402 |
| Upper 20% | 301 (19.3) | 19 (15.7) | 0.7 (0.5–1.2) | 0.171 | 0.7 (0.4–1.2) | 0.255 |
| Father’s occupation | | | | | | |
| Farmer | 1058 (68.0) | 87 (71.9) | Ref | | | |
| Employed | 348 (22.4) | 22 (18.2) | 1.0 (0.5–1.8) | 0.929 | | |
| Unemployed | 150 (9.6) | 12 (9.9) | 0.8 (0.5–1.2) | 0.237 | | |

**Table 3.** *Cont.*

| Characteristics | All N = 1556 n (%) | LBW N = 121 n (%) | Crude RR (95% CI) N = 1556 | *p* Value | Adjusted RR (95% CI) N = 1556 | *p* Value |
|---|---|---|---|---|---|---|
| Domestic water source | | | | | | |
| Tap/Borehole | 977 (62.8) | 72 (59.5) | Ref | | | |
| Spring/river/well/stream/pond | 579 (37.2) | 49 (40.5) | 1.1 (0.8–1.7) | 0.476 | | |
| Intervention | | | | | | |
| No | 740 (47.6) | 60 (49.6) | Ref | | | |
| Yes | 816 (52.4) | 61 (50.4) | 0.9 (0.6–1.3) | 0.656 | 0.9 (0.6–1.4) | 0.716 |
| Facility Delivery | | | | | | |
| No | 482 (31.1) | 42 (34.7) | | | | |
| Yes | 1070 (68.9) | 79 (65.3) | 0.8 (0.6–1.1) | 0.251 | | |
| Maternal clinical characteristics | | | | | | |
| History of a small infant | | | | | | |
| No | 218 (14.0) | 19 (15.7) | Ref | | | |
| Yes | 985 (63.3) | 68 (56.2) | 1.3 (0.7–2.1) | 0.386 | 2.1 (1.2–3.7) | 0.014 |
| Prime gravida | 353 (22.7) | 34 (28.1) | 1.4 (0.9–2.1) | 0.090 | 1.1 (0.6–1.8) | 0.778 |
| Parity | | | | | | |
| Prime gravida | 353 (22.7) | 34 (28.1) | Omitted | | | |
| 1–6 | 1043 (67.0) | 77 (63.6) | Ref | | | |
| 7 or more | 160 (10.3) | 10 (8.3) | 0.8 (0.5–1.5) | 0.573 | 0.6 (0.3–1.4) | 0.226 |
| Maternal HIV infection | | | | | | |
| No | 1455 (93.5) | 116 (95.9) | Ref | | | |
| Yes | 73 (4.7) | 5 (4.1) | 0.9 (0.4–2.0) | 0.723 | 0.9 (0.4–1.8) | 0.719 |
| Unknown | 28 (1.8) | 0 (0.0) | Not applicable | | | |
| Antennal attendance | | | | | | |
| No | 352 (22.6) | 30 (24.8) | Ref | | | |
| Yes | 1204 (77.4) | 91 (75.2) | 0.9 (0.6–1.3) | 0.522 | | |
| IPT for malaria in pregnancy | | | | | | |
| No | 704 (45.2) | 69 (57.0) | Ref | | | |
| Yes | 852 (54.8) | 52 (43.0) | 0.6 (0.4–0.8) | 0.003 | 0.6 (0.4–0.8) | 0.001 |
| Malaria in pregnancy | | | | | | |
| No | 502 (32.3) | 25 (20.7) | Ref | | | |
| Yes | 388 (24.9) | 32 (26.4) | 1.7 (1.01–2.7) | 0.046 | 1.7 (1.01–2.9) | 0.045 |
| Unknown | 666 (42.8) | 64 (52.9) | 1.9 (1.2–3.0) | 0.005 | 1.9 (1.1–3.2) | 0.020 |
| Infant sex | | | | | | |
| Female | 757 (48.7) | 63 (52.1) | Ref | | | |
| Male | 799 (51.3) | 58 (47.9) | 0.9 (0.6–1.2) | 0.393 | 0.9 (0.7–1.2) | 0.463 |

N/n (%) frequency (percentage), RR risk ratio, CI confidence interval, HIV human immunodeficiency virus.

### 3.4.2. Preterm Birth

HIV infection was associated with an increased risk of PB (adjusted or aRR: 2.9, 95% CI: 1.1–7.3) in the multivariable analysis (Table 4). Maternal education (≥7 years) was associated with a reduced risk of PB (aRR: 0.3, 95% CI: 0.1–0.98).

**Table 4.** Bivariable and multivariable analysis of risk factors for preterm birth in northern Uganda.

| Characteristics | All N = 1279 n (%) | PB N = 53 n (%) | Crude RR (95% CI) N = 1279 | *p* Value | Adjusted RR (95% CI) N = 1279 | *p* Value |
|---|---|---|---|---|---|---|
| Maternal characteristics | | | | | | |
| Maternal age | | | | | | |
| 12–19 years | 330 (25.8) | 18 (34.0) | 1.6 (0.9–2.9) | 0.142 | 2.0 (1.0–4.3) | 0.050 |
| 20–34 years | 815 (63.7) | 28 (52.8) | Ref | | | |
| ≥35 years | 134 (10.5) | 7 (13.2) | 1.5 (0.7–3.5) | 0.295 | 1.2 (0.6–2.6) | 0.612 |
| Maternal education | | | | | | |
| 0–6 years | 1032 (80.7) | 50 (94.3) | Ref | | | |
| ≥7 years | 247 (19.3) | 3 (5.7) | 0.2 (0.1–0.8) | 0.022 | 0.3 (0.1–0.98) | 0.047 |
| Maternal vocational education | | | | | | |
| No | 1131 (88.4) | 45 (84.9) | | | | |
| Yes | 148 (11.6) | 8 (15.1) | | | | |
| Marital status | | | | | | |
| Married | 1166 (91.2) | 47 (88.7) | 0.7 (0.3–1.5) | 0.393 | | |
| Single/separated/divorced/widowed | 113 (8.8) | 6 (11.3) | Ref | | | |

**Table 4.** *Cont.*

| Characteristics | All N = 1279 n (%) | PB N = 53 n (%) | Crude RR (95% CI) N = 1279 | *p* Value | Adjusted RR (95% CI) N = 1279 | *p* Value |
|---|---|---|---|---|---|---|
| Wealth index | | | | | | |
| Lower 40% | 574 (44.9) | 26 (49.1) | Ref | | | |
| Middle 40% | 465 (36.3) | 18 (34.0) | 0.8 (0.5–1.4) | 0.513 | 0.9 (0.6–1.5) | 0.815 |
| Upper 20% | 240 (18.8) | 9 (17.0) | 0.8 (0.4–1.9) | 0.650 | 1.1 (0.5–2.5) | 0.847 |
| Father's occupation | | | | | | |
| Farmer | 883 (69.0) | 38 (71.7) | Ref | | | |
| Employed | 274 (21.4) | 8 (15.1) | 1.4 (0.7–2.9) | 0.342 | | |
| Unemployed | 122 (9.5) | 7 (13.2) | 0.7 (0.4–1.4) | 0.305 | | |
| Domestic water source | | | | | | |
| Tap/Borehole | 802 (62.7) | 27 (50.9) | Ref | | | |
| Spring/river/well/stream/pond | 477 (37.3) | 26 (49.1) | 1.1 (0.8–1.7) | 0.476 | 1.5 (0.9–2.6) | 0.121 |
| Intervention | | | | | | |
| No | 601 (47.0) | 23 (43.4) | Ref | | | |
| Yes | 678 (53.0) | 30 (56.6) | 1.1 (0.6–2.1) | 0.670 | 1.2 (0.7–2.2) | 0.517 |
| Facility Delivery | | | | | | |
| No | 397 (31.0) | 23 (4.4) | Ref | | | |
| Yes | 882 (69.0) | 30 (56.6) | 0.6 (0.3- 1.01) | 0.054 | 0.6 (0.4–1.0) | 0.045 |
| Maternal clinical factors | | | | | | |
| History of a small infant | | | | | | |
| No | 964 (75.4) | 39 (73.6) | Ref | | | |
| Yes | 40 (3.1) | 2 (3.8) | 1.2 (0.2–5.7) | 0.927 | 1.0 (0.2–5.2) | 0.986 |
| Prime gravida | 275 (21.5) | 12 (22.6) | 1.1 (0.5–2.0) | 0.884 | 0.8 (0.3–1.8) | 0.557 |
| Parity | | | | | | |
| Prime gravida | 275 (21.5) | 12 (22.6) | Ref | | | |
| 1–6 | 872 (68.2) | 34 (64.2) | 1.1 (0.6–2.1) | 0.790 | | |
| 7 or more | 132 (10.3) | 7 (13.2) | 1.4 (0.7–2.6) | 0.346 | | |
| Maternal HIV infection | | | | | | |
| No | 1205 (94.2) | 47 (88.7) | Ref | | | |
| Yes | 61 (4.8) | 6 (11.3) | 2.2 (0.9–5.6) | 0.094 | 2.9 (1.1–7.3) | 0.026 |
| Unknown | 13 (1.0) | 0 (0.0) | NA | | | |
| Antenatal attendance | | | | | | |
| No | 283 (22.1) | 14 (26.4) | Ref | | | |
| Yes | 996 (77.9) | 39 (73.6) | 0.8 (0.4–1.4) | 0.451 | | |
| IPT for malaria in pregnancy | | | | | | |
| No | 695 (54.3) | 29 (54.7) | Ref | | | |
| Yes | 584 (45.7) | 24 (45.3) | 0.9 (0.5–1.6) | 0.832 | 1.0 (0.6–1.8) | 0.886 |
| Malaria in pregnancy | | | | | | |
| No | 330 (25.8) | 15 (28.3) | Ref | | | |
| Yes | 342 (26.7) | 13 (24.5) | 0.8 (0.5–1.5) | 0.568 | | |
| Unknown | 607 (47.5) | 25 (47.2) | 0.9 (0.5–1.6) | 0.785 | | |
| Infant sex | | | | | | |
| Female | 620 (48.5) | 20 (37.7) | Ref | | | |
| Male | 659 (51.5) | 33 (62.3) | 1.6 (0.9–2.7) | 0.117 | 1.6 (1.0–2.8) | 0.070 |

N/n (%) frequency (percentage), RR risk ratio, CI confidence interval, PB preterm birth, NA not applicable, IPT intermittent preventive treatment, HIV human immunodeficiency virus.

## 4. Discussion

In our cohort, the incidence of LBW was 7.3%. The proportion of LBW in post-conflict rural Northern Uganda is lower than most other estimates, be it the global, sub-Saharan Africa, or Uganda [1,23,24]. This study was a sub-study of a trial in which one of the inclusion criteria was a gestational age 28 or more weeks of pregnancy. Given that women were enrolled at 28 or more weeks, low birthweight occurring before recruitment were systematically excluded. Therefore, our study is likely to have underestimated the true incidence of both LBW.

Factors associated with low birthweight included maternal age ≥35 years, history of a small newborn in the previous pregnancy, maternal malaria in pregnancy and intermittent preventive treatment (IPT) for malaria. The finding that advanced maternal age (≥35 years) was associated with an increased risk of LBW in our cohort is not unique to our report. Numerous studies have described the increased risk of LBW with low or advanced maternal age [25,26]. The study also reports an associated increased risk of LBW among mothers with history of a small newborn, in the most recent pregnancy. Other studies report similar links [17,27].

The relationship between malaria in pregnancy and its association with increased risk of LBW has been reported elsewhere [28]. Similarly, we also report reduced risk of LBW among infants born to mothers who had intermittent preventive therapy for malaria during pregnancy. Malaria IPT during pregnancy reduces placental malaria, a long known risk factor for LBW and preterm births (small newborn) [29].

The preterm birth (PB) proportion in our cohort was 5.0% and is similar to a hospital-based study in Eastern Uganda, with similar inclusion and exclusion criteria [6]. The observed estimate in this cohort, however, is lower than the global, sub-Saharan Africa, or Uganda estimates [5,24].

The low PB proportion observed in our study may be due to the trial eligibility criteria discussed above that could have resulted in exclusion of some preterm births occurring before recruitment into the main trial. Secondly, the NBS for foetal maturation for gestational age determination (instead of mid-pregnancy ultrasound as the gold standard), may have contributed to the underestimation of PB in this cohort. For instance, a study by Sasidharan and colleagues reported that NBS overestimated gestational age (GA) by up to 2 weeks (8 MRTS), with increasing postnatal age [30]. Therefore, if the current global PB modelled estimates by the global burden of disease (GBD) research group are true, we may have over-estimated GA by 3MRTS (1.2 weeks), see our sensitivity analysis in Table 2 above. Although scientists modified the NBS system to identify extremely preterm babies up to seven days of postnatal age, it seems postnatal age at assessment may have played a role in the PB estimates in our cohort. The exclusion of 363/1833 (19.8%) infants not reached for NBS gestational age (GA) assessment within 7 days of postnatal life, and another 191/1833 (10.4%) of the infants without birthweight, may have also resulted in the observed low PB incidence proportion. Despite the challenges faced in PB diagnosis in our setting, the findings may still be relevant in contributing to the pool of knowledge on preterm births and associated risk factors, to guide decision making in a resource-limited post-conflict setting.

Factors associated with an increased risk of preterm birth include maternal HIV infection. Maternal education for seven or more years was associated with a reduced risk. Our finding that low maternal education is associated with an increased risk of PB has been reported elsewhere [31–33]. The increased risk of PBs among HIV infected women, compared to the uninfected has also been documented over the last 3 decades [34].

In our cohort, teenage motherhood doubled the risk of PB and this is of public health importance. The finding is similar to findings from several other studies across the globe [35,36]. Although the biological link between teenage pregnancy and PB is not properly understood, [10,37] pregnant teens are likely to be disfavoured in several aspects such as education, access to care and nutrition compared to older mothers [38–40].

The study also reported an increased risk of PB among male infants, compared to female infants. This may be a methodological artefact due to differences in NBS scoring of the two sexes. An analysis of mean difference for the overall MRTS and individual elements for physical and neuromuscular scores by sex, demonstrated a significant difference in physical maturity rating for breasts. Female infants were systematically over-scored by 0.14 (95% CI: 0.08–0.21) equivalent to 4 days (95% CI: 2–6) points in the physical maturity rating for breasts, which may contribute to fewer infants being classified as being PB. It is still possible that there is still true increase in the risk of PB for male infants as this has been reported elsewhere [19,41].

## 5. Limitations and Strengths

The main limitation of our study is the potential for selection bias at inclusion which may have introduced systematic error. In the main Survival Pluss randomised trial in which our observational study was nested, inclusions were allowed at any time from 28 or more weeks of gestation (WoG). The inclusion of pregnancies from 28 or more WoG is based on foetal viability in our low resource settings. Deliveries before 28 weeks of gestational age are considered abortions (in-service personal experience). It means that a pregnant woman could be included at, for instance, 35 weeks of gestation. This also means that not all pregnant women in the study area were followed up from exactly 28 WoG. Women who had LBW and PB before recruitment into the trial were systematically excluded from our study. This likely caused us to underestimate the true incidence of LBW and PB. This could explain the low incidence of LBW and PB reported in this study.

Furthermore, additional selection biases could have occurred due to loss to follow up resulting from missing birthweight and/or gestational age assessment (GA) of the infants. For the PB, we restricted the analysis to the sample of infants with both GA and birthweight. Approximately 554 infants (30%) of the 1833 in the cohort did not have both birthweight and gestational age measurements and were excluded from the analysis. This could have possibly resulted in a selection bias. That said, in a sensitivity analysis, we found no major differences in socio-demographic characteristics of included and excluded participants. Future studies to estimate the incidence of LBW and PB should aim at enrolling mothers in the first trimester and following up the entire cohort for the remainder of the pregnancy. This would permit more accurate gestational age estimations and provide a more complete cohort.

Albeit the above limitations, there were several strengths in our study. Firstly, we used a community-based cohort—likely to reflect the community at large. Secondly, we were able to follow-up and obtain birthweight within 48 hours on 1556/1833 (85%) of the cohort, minimising the risk of selection bias. Thirdly, mothers were interviewed shortly after the delivery, minimising the likelihood of recall bias. Lastly, we used hard, explicitly defined outcome measures (low birthweight and preterm birth). This reduced the likelihood of misclassification/information bias.

## 6. Conclusions

The incidence of LBW and PB were low, compared to the national, sub-Saharan Africa and global estimates. Advanced maternal age of $\geq$35 years and history of a small newborn were associated with increased risk of low birthweight. Maternal formal education for $\geq$7 years was associated with a reduced risk of PB while HIV infection was associated with an increased risk of PB.

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**Informed Consent Statement:** Written informed consents were obtained from all Survival Pluss study participants. Participant confidentiality was maintained, through use of password protected mobile phones and computers.

**Data Availability Statement:** The data for this manuscript may be access from the corresponding author on reasonable request. The corresponding author's email: beachristo2003@gmail.com and Tel.: +256772896397.

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