Stellenbosch University

Faculty of Health Sciences

Department of Interdisciplinary Health Sciences

Division of Community Health

Research Title**: Trends in mortality and factors associated with mortality and morbidity amongst hospitalized low birth weight infants at a tertiary level hospital in Cameroon, 2001-2015.**

Degree: MSc in Clinical Epidemiology

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Covering Letter

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The Editor
The Lancet Global Health

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A covering letter for the submission of my research article to the Lancet Global Health

Dear Sir/Madame,

I am Alison Wiyeh, a final year student, enrolled in the Master's in Clinical Epidemiology programme, under the Division of Community health, Department of interdisciplinary health sciences of Stellenbosch University, in South Africa.

I wish to submit my research article titled "**Trends in mortality and factors associated with mortality and morbidity, amongst hospitalized Low birth weight infants at a tertiary level hospital in Cameroon 2001-2015**" to your journal for publication.

In this article, we describe a retrospective cohort study that examines the trend in mortality rate of low birth weight infants in Cameroon, and identifies risk factors associated with their mortality and morbidity. It is an original article, with focus on neonatal health in a middle income country, hence meets the description of the types of articles published in your journal.

I will be highly honored if given the opportunity to publish my research paper in your journal. This publication will contribute to the pool of existing evidence in the field of neonatology and hopefully shape policy with regards to the health care of low birth weight infants.

Sincerely

Alison Beriliy Wiyeh

Part A: Completed manuscript

Title page

Trends in mortality and factors associated with mortality and morbidity amongst hospitalized low birth weight infants at a tertiary level hospital in Cameroon, 2001-2015.

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Abstract

Background: Babies born with a birth weight of less than 2500grams have a low birth weight (LBW) and death amongst them accounts for 80% of all neonatal deaths. At the endpoint of the Millennium Development Goals (MDGs), we evaluate the progress made by Laquintinie hospital, Cameroon in reducing mortality amongst low birth weight babies, and identify factors associated with their morbidity and mortality.

Methods: We estimated the mortality rates amongst LBW infants from 2001 to 2015, using a retrospective cohort study. Hospital records from 2001 to 2014, and the medical files for 2015 of LBW infants hospitalised in this hospital were used to evaluate their outcomes and factors associated with their morbidity and mortality.

Findings: The overall mortality rate progressively increased from 19·9% in 2001 to 50·7% in 2015, with the greatest increase observed amongst extremely low birth weight infants (ELBW). In time series analysis, ELBW infants β: 0·49 (95% CI 0.12 - 0.87) and incremental year of birth β: 1·4 (95% CI 1.04 - 1.81) accounted for the increase in mortality rate. ELBW (OR: 4·3, 95% CI), VLBW (OR: 2·7, 95% CI) and apgar <7 at 5 minutes (OR: 25, P=0·022) were risk factors for respiratory morbidity. Apgar <7 at 5 minutes (OR: 5·5, P<0·001) was a risk factor for neurological morbidity. Factors associated with mortality were VLBW (OR: 4·7 P<0·001), respiratory distress (OR: 9·2, P<0·001), apnoea (OR: 4·2, P0·004) and gastrointestinal haemorrhage (OR: 5·839, P<0·001).

Interpretation: The mortality rates amongst low birth weight infants hospitalised at Laquintinie Hospital, increased in the period 2001-2015, and negatively impacted its achievement of MDG 4.

Funding

Introduction

The World Health Organisation (WHO) defines low birth weight (LBW) as a birth weight of less than 2500 grams.[1] Subcategories include very low birth weight (VLBW) and extremely low birth weight (ELBW), with birth weights of less than 1500 grams and 1000 grams respectively.[2] Low birth weight occurs either due to prematurity or intrauterine growth restriction.[2] About 15% of the world's 20 million low birth weight babies are born in Sub-Saharan Africa.[3] These new-borns experience a lot of complications at birth, and are 20 times more likely to die than compared to heavier babies.[3]

During the Millennium Development Goals (MDGs) period, there was a reduction of about 50% in child mortality globally.[4] However neonatal deaths still account for 44% of death in children under 5 years with evidence of a slight decline over the past 15 years.[5] Hence reductions in neonatal death rates (age <1 month) are lagging behind those for children aged 1 - 59 months.[6] In 2012, estimates suggested that more than 80% of deaths in the neonatal period in sub-Saharan Africa and South Asia, occurred in babies born with a low birth weight.[7]

The population of Cameroon was projected to be 22,179,707 inhabitants in 2015 distributed in 10 regions. Data suggests that at least 11% of new-borns in Cameroon have a low birth weight.[2] The 2011 demographic and health surveys for Cameroon revealed that neonatal mortality experienced only a slight decrease from 36% in the 90s to 31% in 2011.[8] Studies carried out in Cameroon so far confirm that newborns with a birth weight of less than 2500 grams constitute a great percentage of children who die during their first 4 weeks of life.[9,10] At the Yaoundé Gynaeco-Obstetric and Paediatric Hospital, 64% of all neonatal deaths were as a result of low birth weight of less than 2500 grams.[11]

The fourth MDG aimed at reducing child mortality by striving for a two thirds reduction in under-five mortality rate between 1990 and 2015. One of the indicators used was the infant

mortality rate which comprises both neonatal and post neonatal mortality.[12] The third Sustainable development goals (SDG) aims to end preventable deaths of newborns, with a target neonatal mortality rate of at least as low as 12 per 1,000 live births.[13] As we transit to the SDGs it will be important to know the mortality rates and identify risk factors for morbidity amongst LBW infants as they make up an important proportion of neonates.

The main aim of this study was to describe the trends in the mortality of low birth weight infants hospitalized at the Laquintinie Hospital in Douala, Cameroon between 2001-2015, and identify factors associated with mortality and morbidity in 2015. Secondary objectives were to describe the maternal, obstetric and fetal characteristics of babies hospitalized in 2015.

Research in context

Evidence before this study: The prevalence of low birth weight is higher in developing countries then developed countries. There is a 20 fold increase in the risk of mortality amongst infants weighing less than 2500g, compared to their heavier counterparts.

Added value of this study: This study highlights the trends in mortality rate in low birth weight infants in a middle income country during the millennium development goals, and identifies risk factors for mortality and morbidity.

Implications of all the available evidence: The totality of the available evidence will serve to raise awareness on the increase in the poor outcomes of low birth weight infants. It will also motivate health care providers and policy makers to design and implement measures that target specific problems, amongst this group of infants, in settings with limited resources.

Methods

Design: We carried out a retrospective cohort study, with data collected between February and July 2016.

Setting of the study

It was done at the Laquintinie Hospital, the main referral hospital in the city of Douala, in the Littoral province of Cameroon. This hospital receives the highest number of patients in this city per year.

Eligibility criteria

Our study population consisted of LBW infants (born before 37 weeks), hospitalized in the neonatal unit of the Laquintinie hospital Douala, Cameroon between the 1st of January 2001 and the 31st of December 2015. The gestational age was determined either from the mother's last menstrual period, first trimester ultrasound, or physical examination by a pediatrician using the Ballard score. Infants with a birth weight > 2500g were excluded.

Data collection

We used the hospital records of the neonatal unit, containing details on all neonates admitted in the unit between 1st of January 2001 and 31st of December 2015. We used a predesigned and tested data collection form to collect anonymized information on the patient's gender, birth weight, place of birth, weight on discharge, duration of hospitalization and the outcome on discharge from the hospital. For newborns hospitalized in the year 2015, we used both the hospital records and the patient's individual hospital files, from where we collected anonymized data on the maternal characteristics (age, educational level, parity and HIV status), obstetric characteristics (method of delivery and number of children), fetal characteristics such as the gender, apgar score at 5 minutes, place of birth, delay between delivery and

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hospitalization. For each patient, all laboratory investigations carried out were noted and complications present at admission as well as those diagnosed during hospitalization were recorded. Missing outcomes were defined as outcomes that were not filled in the records. Mortality rate was defined as the number of deaths amongst all low birth weight babies hospitalized between 2001 and 2015. We defined morbidity as the complications reported from the time of birth till the infants were discharged from hospitalisation. These complications were stratified by birth weight category. We identified factors associated with selected morbidities in 2015. These were respiratory morbidity (respiratory distress + apnea), gastrointestinal morbidity (NEC+GIT haemorrhage), and neurological morbidity (asphyxia + convulsions).

The data was entered into Microsoft Excel 2010 and analysed using Stata/IC version 14. A time series analysis was done by multiple regression using the Newey-West estimator. Multiple logistic regression analysis was used to assess factors associated with mortality and morbidity in the 2015 cohort. Independent variables were selected from results of bivariate analyses. Those variables associated with mortality and morbidity at the 90% level of significance or higher were entered into a backwards stepwise model. Likelihood ratios were used to test models with entry and removal probabilities set at 0·1 and 0·05 respectively.

Role of the funding source

We received no external funding for this study. The corresponding author had full access to all the data in the study and had final responsibility for the manuscript submission for publication.

Results

General characteristics

There were 7007 low birth weight babies hospitalised at the Laquintinie hospital during the study period, with 50·9% being females and 47·6% being male. The gender was unknown in 1·5% of babies. Babies in the birth weight category 1500-2499 made up 72·9% of the all low

birth weights and those with a birth weight of less than 1000g constituted the smallest population of only 3·4%. These results are summarised in table 1.

Figure 1 illustrates that the total number of low birth weight infants hospitalized progressively increased during the MDG period by almost 40%, with the highest numbers recorded in 2011 (610) and the lowest in 2004 (285).

The increase in the number of low birth weight was in all birth weight categories, with the highest being amongst the LBW, as illustrated in figure 2.

Trends in outcomes

From the hospital registries, there were 4 possible outcomes described: dead, alive, discharged against medical advice (DAMA), or unknown outcome. Compared to 2001, there were more infants being discharged from the hospital against medical advice in 2015. The mortality rate gradually increased over from 19.9% in 2001 to 50·7% in 2015. However, in figure 3, we note that the amount of unknown outcomes peaked in 2005 and gradually decreased to its lowest in 2015, indicating an improvement in the management of data in 2015 compared to the previous years. Figure 4 sheds more light on the trends in the death rates during the study period. Mortality rate amongst all birth weight categories increased. However, contrary to the rates of hospitalisation, the highest death rates were recorded amongst ELBWs and the lowest mortality rates amongst those with a birth weight between 1500g and 2499g (figure 4).

The neonates were aggregated according to their month and year of birth, and a time series analysis was performed on the outcome of mortality percentage per month using multiple linear regression with Newey-West t statistic test. Findings showed that 2·07 less patients died with each additional day of hospitalisation ($p<0·001$) after adjusting for the effects of the year of birth and the proportion of ELBW neonates. Also, with each additional year of birth 1·4 more

patients died when other variables were kept constant (p<0·001). However, this was confounded by the effect of being born with ELBW (table 2). For every one percent increase in the proportion of ELBW neonates, 0·5 patients died when other variables were kept constant (p=0·011). Hence, although the increase in mortality rate over time was a partly a result of an increase in the EBLW babies there were probably other explanatory factors which were not measured in this study.

For the year 2015, we summarized some socio demographic and obstetric characteristics of the mothers as well as clinical characteristics of newborns. The majority of mothers whose educational level was known had attained at least a secondary level of education. 83% were known to be HIV negative. More mothers (69·3%) gave birth vaginally with most of them delivering in the hospital where our study was carried (51·4%). The majority (65·6%) of the deliveries were singleton deliveries and 92·5% of all low birth weight babies were classified as being premature (Table 3).

In 2015, the most common complications were respiratory distress (62·2%), confirmed infections (46·7%), anaemia requiring blood transfusion (30·6%), jaundice requiring phototherapy (29·2%), and apnoea (16·1%). Respiratory distress and apnoea were more prevalent amongst the ELBW babies and decreased as the birth weight increased, while infections, jaundice and anaemia were more common amongst babies in the category 1500-2499g (Table 4).

Factors associated with mortality and morbidity in 2015

The majority of deaths (79·1 %) occurred in the early neonatal period (0-7 days). On bivariate analysis, birth weight, place of birth, HIV status, method of delivery, laboratory investigations, respiratory distress, infections, jaundice, apnea and GIT haemorrhage were associated with mortality. However, after multivariate analysis with logistic regression, only birth weight, apnoea, GIT haemorrhage and respiratory distress remained significantly associated with

mortality. Babies with respiratory distress were 9·2 times more likely to die compared to those without respiratory distress after adjusting for other variables in the model. The mortality amongst babies with a longer period of hospitalisation was reduced by 16·6 % (Table 5).

In 2015, birth weight and apgar score of less than 7 were associated with an increased risk of respiratory morbidity, while babies with an apgar score of less than 7 were 5·5 times more likely to suffer from neurological morbidity (table 6). Patients who had laboratory investigations were 0·54 times less likely to suffer from GIT morbidity.

Discussion

Our study examines the trends in the outcomes of low birth weight neonates hospitalised at Laquintinie hospital during the period of the MDGs, with specific interest in the mortality. It also examines factors associated with mortality and morbidity amongst LBWs hospitalised in 2015. This study finds that the mortality rates amongst low birth weight babies hospitalised at Laquintinie Hospital, in Cameroon, increased in the period 2001-2015. The risk factors for mortality in 2015 were extreme and very low birth weight, respiratory distress, apnoea and gastrointestinal haemorrhage. The main risk factors for respiratory morbidity were extreme low birth weight, very low birth weight and Apgar score <7 at 5 minutes. An apgar score of <7 at 5 minutes was associated with neurological morbidity and infants who underwent paraclinical investigations were less likely to suffer from gastrointestinal morbidity.

Interestingly, although data obtained from Demographic and health surveys suggest that there has been a decrease in the incidence of low birth weight[14] nationwide, our findings reveal an overall increase in the number of low birth weight neonates hospitalised between 2001 and 2015 in all birth categories especially amongst neonates in the 1500-2499g category with the majority being females. Fondjo had similar findings with the majority of neonates weighing between 1500-2000g.[15] Nlend *et al* found a decrease at the Essos hospital in Yaounde.[16] However they included only ELBW and VLBW neonates in their study.

Overall the mortality rate increased, with the highest rates being in the ELBW category. In 2015, the majority of deaths (79·1%) occurred in the early neonatal period. Mungyeh *et al* observed a decrease in mortality rates.[11] They associated this decrease to factors such as the institution of a minimum package of laboratory investigations which has improved the management of patients. The patients in our study site do not have access to these advantages and have to pay out of pocket for the health care of their babies. The neonatology unit has a shortage of vital equipment such as incubators, and important medications such as exogenous surfactant. Almost half of the babies hospitalised in this unit in 2015 were born in other external health facilities. The antenatal care (ANC) of the mothers and delivery of these babies in external health facilities may not be optimal. Importantly, in addition to the mortality and survival rates reported by other authors, we report on the rates of missing outcomes, which decreased during the MDGs, implying the medical records of this hospital were more complete. This may have created a false increase in mortality rates over the years as the outcomes of patients were more complete as we moved from 2001 to 2015.

The number of patients discharged against medical advice increased during the period of the MDGs. This could be as a result of financial reasons as most patients lack medical insurance, and a decline in parent's trust on medical care providers amongst others reasons.[17]

For the factors associated with mortality, respiratory distress had the strongest association. Our findings are similar to those of Afjeh *et al.*[18] This is attributed to the non-use of exogenic surfactant, lack of mechanical ventilation. Other identified factors identified include GIT haemorrhage, apnea and VLBW. Similar findings were again reported by Afjeh et al.[18] GIT haemorrhage has been attributed to digestive disorders ranging from feeding intolerance to necrotising enterocolitis (NEC).[19]

Infants born with extremely low birth weight, very low birth weight and apgar <7 at 5 minutes, were at a greater risk of respiratory morbidity. The findings reported by Altman *et al* suggest

that an apgar <7 at 5 minutes and lower gestational age are associated with respiratory morbidity.[20] Though their study was carried out in a setting with more resources, their findings are similar to ours, as the majority (92.5%) of low birth weight in our study was as a result of preterm delivery.

Infants with an apgar <7 at 5 minutes were at risk factor for neurological morbidity. Several studies have reported the association of a poor apgar score and neurological complications. [21,22] In this study, we defined neurological morbidity as reported cases of asphyxia and convulsions because cranial ultrasounds and cerebral CT scans are seldom done by the low birth weight infants in this hospital.

There were limitations to our study. This was a retrospective review of medical records and the study only captures what was recorded in the medical notes. Also, only the data for 2015 was used to identify risk factors for mortality and morbidity. These factors limit the generalizability of the findings to other years. There was a potential risk for information bias, as our study was based on medical records that may have been inaccurately kept, with incomplete data.

The Government needs to strengthen already existing interventions such as maternal access to affordable, accessible and appropriate antenatal care and positive impacting of health behaviours of pregnant women, so as to reduce the incidence of low birth weight. In order to reduce the rates of mortality and morbidity amongst low birth weight babies, obstetric and neonatal health systems, need to be strengthened. There is the need for employment and frequent training health care providers working in these units. The neonatology unit needs to be better equipped and use of vital medications such as exogenous surfactant, which are currently not used in this unit need to be instituted.

There is a huge burden of preventable morbidity and mortality among LBW infants in this unit, and our work enables further research on the determinants of mortality and morbidity amongst

these infants. We recommend further investigation on the role played by economic factors, as well as the structure of the health system on the mortality rate of LBW infants. Studies should focus on identifying cost effective interventions that work in reducing mortality and morbidity amongst LBW infants in low resource settings. Challenges faced in the implementation of interventions such as Kangaroo mother care that are already know to improve the outcomes of LBW infants should be identified and specific solutions should be sought.

List of Abbreviations

ANC: Antenatal care; ELBW: Extremely low birth weight; GIT: Gastrointestinal; MDGs: Millennium development goals; NEC: Necrotizing enterocolitis; SDGs: Sustainable development goals; UNICEF: United Nation International Children Emergency Fund; VLBW: Very low birth weight; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from the institutional review board of the Faculty of Medicine and Pharmaceutical sciences (FMSP) of the University of Douala, Cameroon and the Faculty of Medicine and Health sciences of Stellenbosch University, Cape Town, South Africa. Written authorizations were also obtained from the Director of the hospital and the head of the Paediatrics unit of the Laquintinie Hospital, Douala. We were granted a waiver of informed consent as the study was a record review.

Consent for publication: Not Applicable

Availability of data and material

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Declaration of interests: All authors declare that they have no conflict of interest.

Authors' contribution

AW: Study conception and design, acquisition of data, data analysis and interpretation, manuscript writing and revisions DK: Study conception and design, data interpretation, manuscript writing and revisions. SY: acquisition of data, manuscript revisions. TE: Study conception and design, data analysis and interpretation, manuscript writing and revisions.

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Tables

Table 1: Distribution of low birth weight babies according to birth weight subcategories

Categories	Frequency (%)	Mean (SD)
<1000g	235 (3·4)	834·5 (156·1)
1000-1500g	1672 (23·9)	1260·8 (139·6)
1500-2499g	5100 (72·8)	1887·6 (255·1)
Total	7007 (100·0)	1702·7 (386·8)

Table 2: Time series analysis for variables associated with mortality 2001-2015

Predictor variable	Regression Coef.	Newey-West Std. Err.	P>|t|	95% CI	
				Lower	Upper
Duration of hospitalisation	-2·070637	0·2613553	<0·001	-2·586431	-1·554844
Year of birth	1·428017	0·1976537	<0·001	1·037941	1·818093
Birth weight<1000g	0·4943751	0·1913645	0·011	0·1167107	0·8720395

Table 3: General summary of characteristics for all LBW neonates in 2015

Characteristic	Absolute number	Percentages
Gender Female	267	46·4%
Male	285	49·5%
Unknown	24	4·2%
Education Primary	26	4·5%
Secondary	111	19·3%
Tertiary	62	10·8%
Unknown	377	65·5%
HIV status negative	478	83·0%
positive	46	8·0%
unknown	52	9·0%
Method of delivery CS	111	19·3%
unknown	66	11·5%
vaginal	399	69·3%
Place of birth (HLD?) no	239	41·5%
unknown	41	7·1%
yes	296	51·4%
Delay between birth and admission no	239	81·3%
unknown	41	10·2%
yes	296	8·5%
Preterm delivery no	4	0·7%
unknown	39	6·8%
yes	533	92·5%
Number of children 1	330	65·6%
2	169	33·6%
3	4	0·8%
apgar <7	63	10·9%
>=7	359	62·3%
missing	154	26·7%

Table 4: Complications developed during hospitalisation in 2015

| Complication	<1000g %(n)	1000-1499g %(n)	1500-2499g %(n)	Total %(n)
Asphyxia	2·3% (1)	9·3% (13)	7·6% (30)	7·6% (44)
Respiratory Distress	83·7% (36)	75·7% (106)	55·0% (216)	62·2% (358)
Suspicion of infection	37·2% (16)	32·1% (45)	20·9% (82)	24·8% (143)
Infection	7·0% (3)	37·1% (52)	54·5% (214)	46·7% (269)
Jaundice with phototherapy	2·3% (1)	20·0% (28)	35·4% (139)	29·2% (168)
NEC	7·0% (3)	6·4% (9)	7·9% (31)	7·5% (43)
Anaemia with transfusion	9·3% (4)	31·4% (44)	32·6% (128)	30·6% (176)
Post IV abscesses	0·0% (0)	6·4% (9)	7·4% (29)	6·6% (38)
Apnea	37·2% (16)	22·1% (31)	11·7% (46)	16·1% (93)
GIT Haemorrhage	11·6% (5)	11·4% (16)	9·7% (38)	10·2% (59)

Table 5: Factors associated with mortality of LBWs in 2015

Variable	Wald	Degree of freedom	P value	OR	95% C.I. for OR	
					Lower	Upper
ELBW vs. LBW	3·597	1	0·058	5·530	0·945	32·382
VLBW vs. LBW	16·831	1	0·000	4·722	2·249	9·913
Respiratory distress	45·998	1	0·000	9·274	4·872	17·653
Apnoea	8·072	1	0·004	4·281	1·570	11·673
GIT haemorrhage	12·309	1	0·000	5·839	2·179	15·646
Duration of hospitalisation	44·842	1	0·000	0·834	0·791	0·880

Table 6: Factors associated with morbidity of LBWs in 2015

| Morbidity	Variable	Wald	df	Sig.	OR	95% C.I. for OR	
						Lower	Upper
Respiratory morbidity	Birth weight <1000g	6·533	1	0·011	4·301	1·405	13·162
	Birth weight 1000-1499g	13·690	1	0·000	2·735	1·605	4·662
	Apgar less than 7	5·225	1	0·022	2·533	1·142	5·622
Neurological morbidity	Apgar less than 7	20·775	1	0·000	5·519	2·648	11·505
GIT morbidity	Patients who had laboratory investigations	4·401	1	0·036	0·543	0·307	0·961

Figures
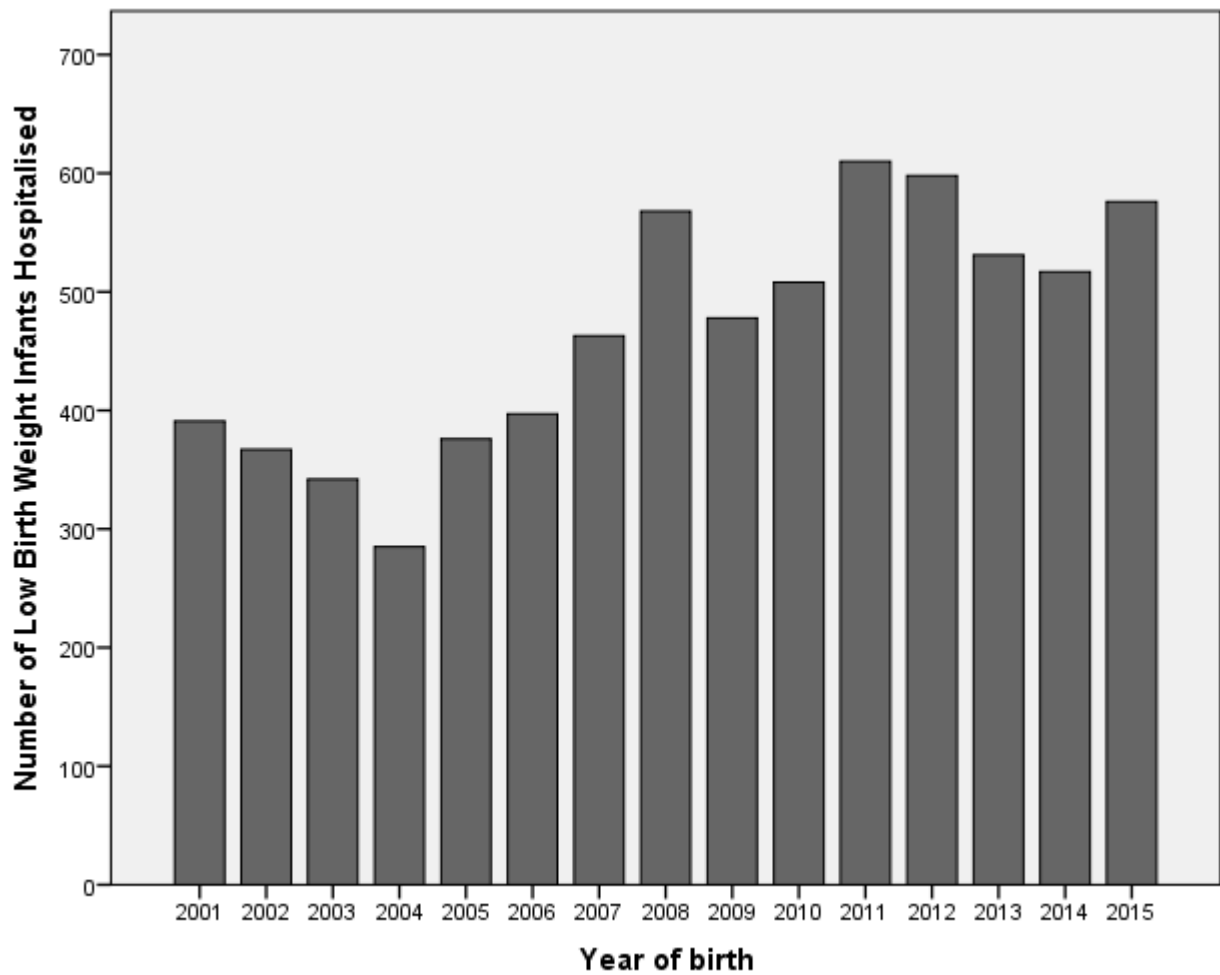
Figure 1: Annual distribution of the number of low birth weight infants hospitalised from   2001-2015
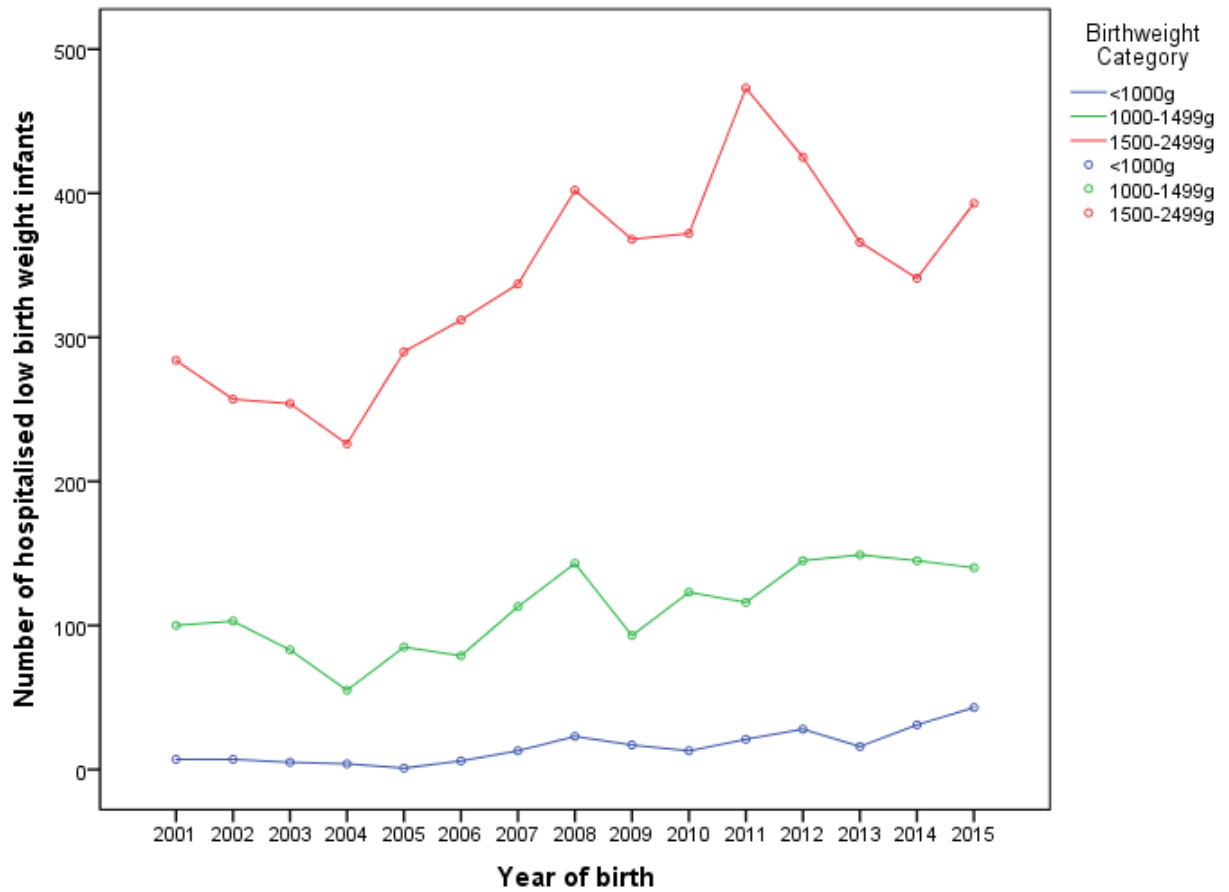
Figure 2: Annual distribution of the number of hospitalised low birth weight infants by birth weight category
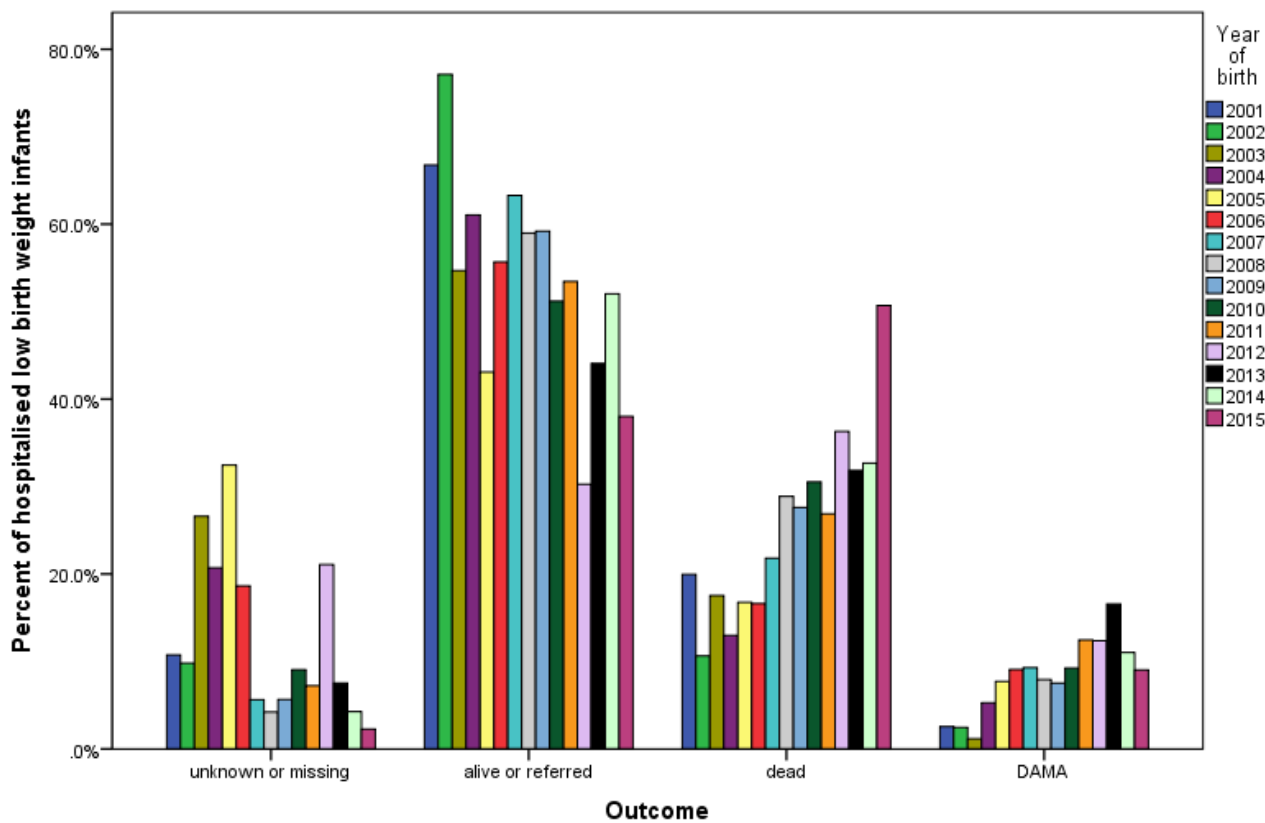
Fig 3: Annual percentages of hospitalised low birth weight infants showing incomplete data, survival rates, mortality rates and DAMA .
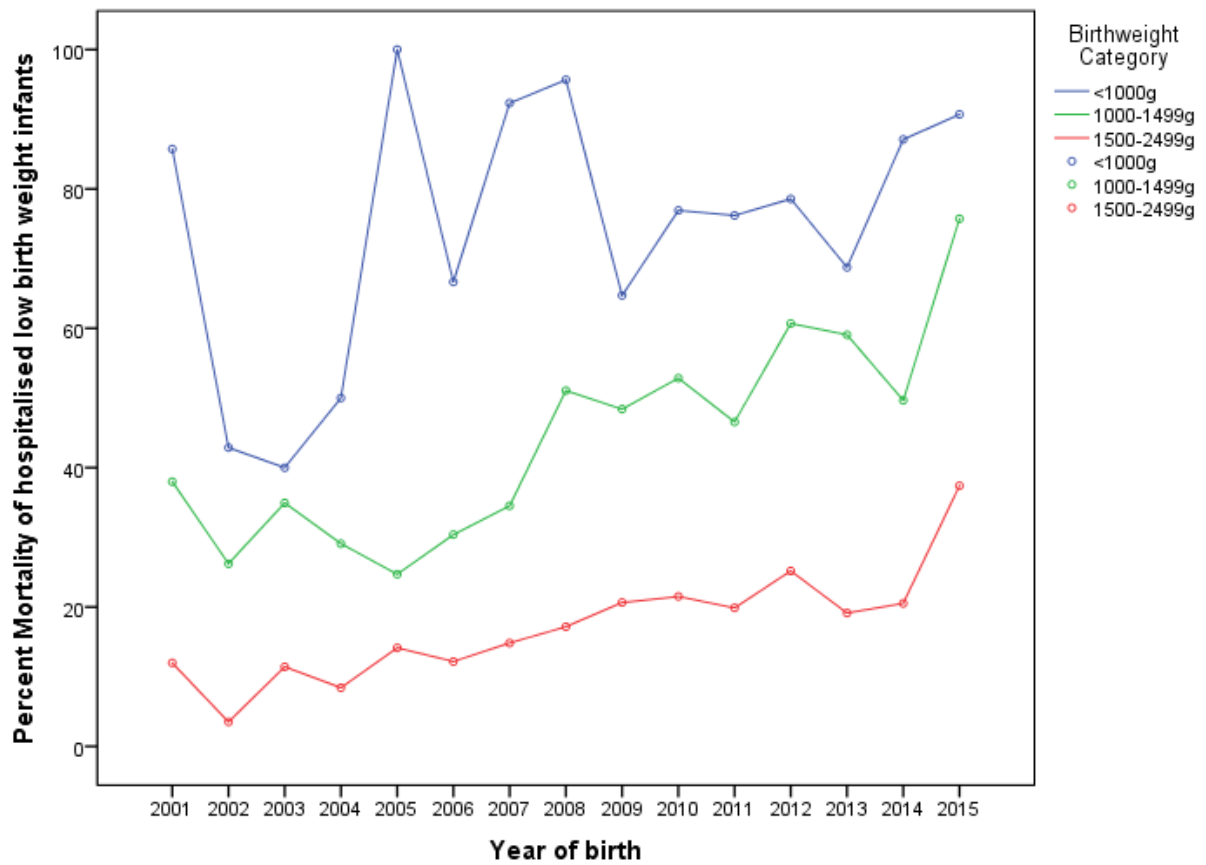
Fig 4: Trends in the mortality rate by birth weight subcategories.

Supervisor Forms

STELLENBOSCH UNIVERSITY
FACULTY OF MEDICINE AND HEALTH SCIENCES

TO WHOM IT MAY CONCERN

ASSIGNMENT/THESIS/DISSERTATION RELEASE

Student's surname	Wiyeh		
Initials	ABW	Student no	SU19215975
Title of assignment/thesis/dissertation: Trends in mortality and factors associated with mortality and morbidity, amongst hospitalized Low birth weights at a tertiary level hospital in a middle income country 2001-2015			
Faculty	Faculty of Health Sciences		
Division/Department	Division of Community Health Department of Interdisciplinary Health Sciences		
Degree	MSc in Clinical Epidemiology		
Supervisor (s)	Tonya Esterhuizen		

I confirm that

- I and the co-supervisor(s) (if applicable) have read the final draft of the assignment/thesis/dissertation
- The assignment/thesis/dissertation is ready for examination
- The assignment/thesis/dissertation has been checked using anti-plagiarism software

Supervisor signature: **Date:**

30/08/2016

_____   _____

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FACULTY OF MEDICINE AND HEALTH SCIENCES

TO WHOM IT MAY CONCERN

ASSIGNMENT/THESIS/DISSERTATION RELEASE

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Faculty	Faculty of Health Sciences
Division/Department	Division of Community Health Department of Interdisciplinary Health Sciences
Degree	MSc in Clinical Epidemiology
Supervisor (s)	Dr. Danielle Christiane Kedy Koum

I confirm that

- I and the co-supervisor(s) (if applicable) have read the final draft of the assignment/thesis/dissertation
- The assignment/thesis/dissertation is ready for examination
- The assignment/thesis/dissertation has been checked using anti-plagiarism software

Date: 30. 08. 2016

Supervisor signature:

Dr KEDY

Part B: Appendices

Research Protocol

Stellenbosch University

Faculty of Health Sciences

Department of Interdisciplinary Health Sciences

Division of Community Health

Research Title**: Trends in mortality and factors associated with mortality and morbidity, amongst hospitalized low birth weight infants in a tertiary level hospital in Cameroon during the period of the Millennium Development Goals 2001-2015**

Degree: MSc in Clinical Epidemiology

Student Name: Alison Beriliy Wiyeh

Student Number: 19215975

Supervisors: 1. Tonya Esterhuizen

2. Dr Danielle Christiane Kedy Koum

Executive Summary

The fourth of the eight Millennium Development Goals aimed at reducing child mortality by two thirds by the year 2015. Globally, statistics suggest that death amongst low birth weight infants account for about half of all deaths in newborns. A renewed understanding and assessment of the outcomes for babies born with a low birth weight is mandatory for implementation of strategies aimed at reducing their morbidity and mortality rate in our health facilities.

This retrospective, descriptive and analytic cohort study will be carried out in Laquintinie hospital, which is a tertiary level hospital in Douala, the economic city of Cameroon. We will use a pre-structured data collection form to extract information from the medical records of low birth weight infants hospitalized in this hospital between the 1st of January 2001 and the 31st of December 2015.

The project outputs will be to describe the trends in mortality and morbidity in low birth weight infants over the past 15 years and to identify potential risk factors for morbidity and mortality. This will be achieved by analytic statistics carried out to look for associations between measured variables and the two outcomes (mortality and morbidity).

The impact of the project will be significant on the hospital as it will set a base for improvement in the management of its low birth weight infants. It will also serve as information to policy makers and help to contribute to scientific knowledge.

Background and Rationale

The World Health organisation defines low birth weight (LBW) as a birth weight of less than 2500 grams.[1] Subcategories include very low birth weight (VLBW) and extremely low birth weight (ELBW), with birth weights of less than 1500 grams and 1000 grams respectively.[2] Low birth weight occurs either due to prematurity or intrauterine growth restriction.[2] About 15% of the world's 20 million low birth weight babies are born in Sub-Saharan Africa.[3] These new-borns experience a lot of complications at birth, and are 20 times more likely to die than compared to heavier babies.[3]

In the year 2000, eight goals were established following the summit of the United Nations. The fourth goal aimed at reducing child mortality by striving for a two thirds reduction in under-five mortality rate between 1990 and 2015 [23]. This was to be monitored by measuring

- ✓ the under-five mortality rate,
- ✓ infant mortality rate and
- ✓ the proportion of 1 year-old children immunized against measles [24].

Fifteen years after the MDGs, a critical evaluation reveals that there has been some improvement made with regard to child health [25]. The global under-five mortality rate has dropped from 90 to 43 deaths per 1,000 live births between 1990 and 2015, hence a decrease of more than half. Subsaharan africa experienced a decrease of 52% in under five mortality falling short of the target set by the MDGs [26]. Interestingly, despite the high under-five mortality rate, it has been observed that the rate of decline was over five times faster during 2005–2013 than the preceeding years [25].

However, the WHO estimates suggest that of the almost 6 million children who die before their fifth birthday in 2015, 1 million will take their first and final breath on the day they are born[25]. An additional 1 million will die in the first week, and around 2.8 million will die during their first 28 days of life (the neonatal period) [25]. There has been a decline in the global neonatal mortality rate of only about 42% between 1990 and 2015, implying that the decline in neonatal mortality is lagging behind when compared to the decline in mortality for children aged 1–59 months [27].
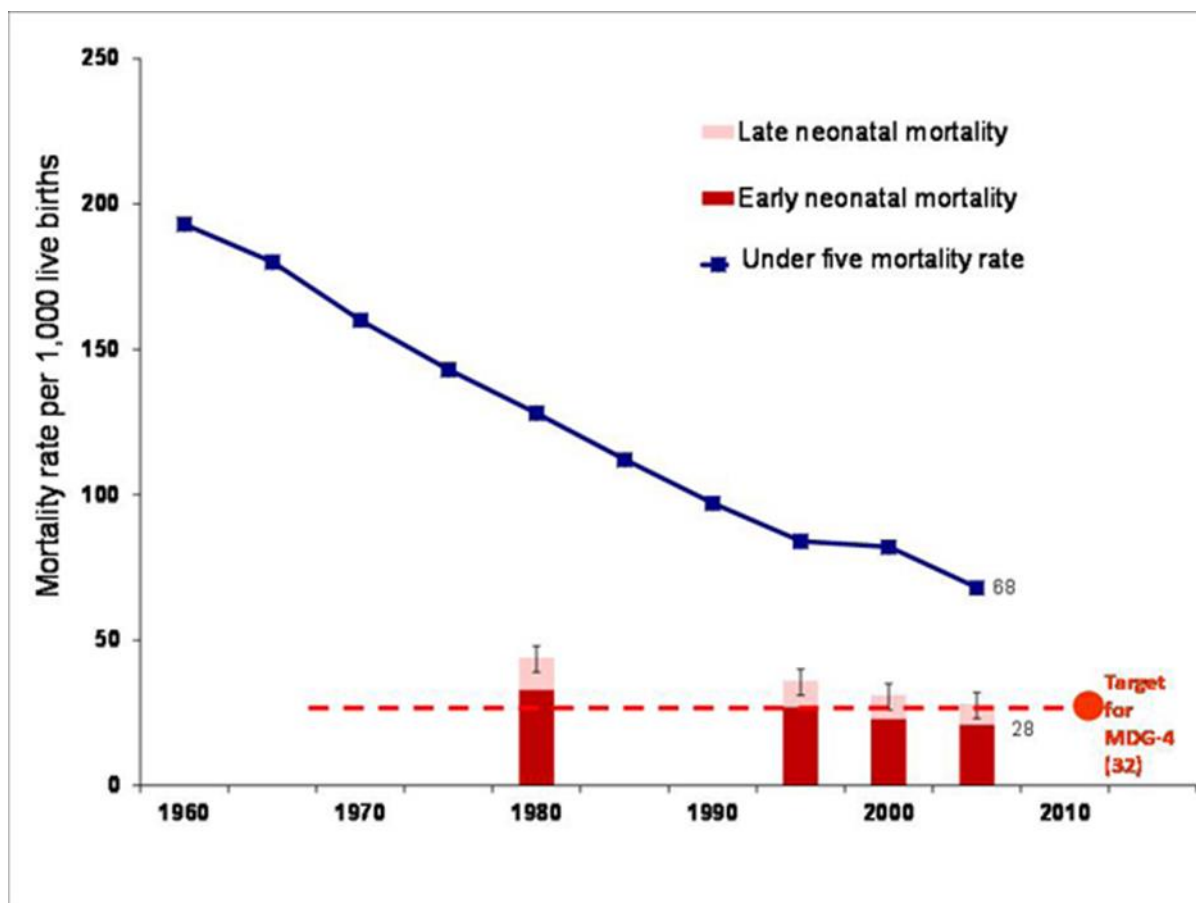
Fig 1: Early and late neonatal mortality rates and under 5 mortality rates per 1000, 1960-2007. Data from UN databases updated to 2007 [27].

Worldwide neonatal deaths now represent a larger share of total under-five deaths. Studies reveal that about 75% of neonatal deaths occur in the first week of life and approximately 35% are attributed to preterm birth, making prematurity the leading cause of neonatal death and the second leading cause of death in children under five years old [28]. It is becoming evident that one important barrier to progress for MDG 4 over the past years has been the failure to reduce neonatal deaths (deaths in the first four weeks of life). Most child survival programmes have targeted other causes of death after the first 4 weeks of life such as pneumonia, diarrhea, and malaria and vaccine preventable conditions. Unfortunately, neonatal causes have not been adequately addressed [27].

One lesson that we have learned from the MDGs is the power of accurate and up to date data. In the process of evidence-based decision-making, the reliable data can be used to develop and implement successful interventions, track performance and improve accountability[25].

It is becoming more evident that for an efficient reduction in child mortality, resources need to be directed toward the leading causes of child mortality, with particular attention focusing on infectious and neonatal causes (6).

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This study will serve as a tool from which policy makers and stake holders can make right decisions and implement efficient strategies to ameliorate the health of the low birth weight infants in Laquintinie hospital. The post MDG era will still be plagued by the same problems faced before the MDGs if we do not assess what has been achieved so far, so as to set goals for what needs to be done. Continued efforts to gather high-quality data and enhance estimation methods are essential for the improvement of future estimates.[29]

For change to occur, it does not just suffice for goals to be set at the national level. They need to be implemented both at the national level and the various health facilities. This study will evaluate the trend in mortality and morbidity amongst low birth weight infants over the past 15 years to see if we have had any improvement. Recent recommendations advise that in all regions, deaths in the neonatal period, primarily due to preterm delivery, sepsis or pneumonia, and birth asphyxia should also be addressed [30].

Considering that deaths due to low birth weight make up a great part of neonatal deaths, a renewed understanding and assessment of the outcomes for these infants is mandatory. The data obtained from this study will help to determine the relative contribution of low birth weight to the burden of disease in children hence inform the planning of healthcare interventions to address this burden. We need to assess the outcome of low birth weight babies in our health facilities and use the data obtained to develop intervention packages aimed to save lives and improve health. [31]

Research aim and hypotheses

Aims:

1. To determine the mortality and morbidity rate of low birth weight infants hospitalized at the Laquintinie Hospital in Douala Cameroon
2. To identify factors associated with mortality and morbidity in low birth weight infants

Specific objectives

✓ To describe the socio demographic and obstetric characteristics of the mothers of the low birthweight infants
✓ To describe the clinical characteristics and investigations of the low birth weight infants during hospitalization
✓ Examine the trend of outcomes (complications of prematurity, mortality) in low birth weight newborns hospitalized in HLD during the study period (MDG period (2001-2015)
✓ Identify factors associated with mortality and morbidity.

Study design and methodology

Study design:

It will be a retrospective cohort study that will be both descriptive and analytical. We will identify the medical records of low birth weight infants hospitalized from 2001 to 2015. It will be a descriptive study as it will be a survey of hospitalized infants who meet the inclusion criteria. It will also have an analytic component as we will try to establish time trends for the various outcomes of interest using statistical methods.

Methodology:

Study Population:

Low birth weight newborns hospitalized in the pediatric unit of the Laquintinie reference hospital from the 1st of January 2001 to the 30th of December 2015. The Laquintinie hospital is located in the city of Douala, which is the economic capital of Cameroon and is the main tertiary level referral hospital. In terms of patient capacity, it receives the highest number of patients in the city of Douala per year.

Sample Size:

We will do consecutive sampling, as of all low birth weight infants hospitalized in this hospital, we will be focusing only on the low birth weight infants hospitalized between the years 2001 and 2015 which was the period set aside for the MDGs. For the sake of the trends as well, all low birth weight newborns hospitalized in the pediatric unit of the Laquintinie hospital whose medical records are available will be included in the study. We anticipate a sample size of about 2250 preterm babies because averagely, 150 low birth weight babies are seen per year, for a total period of 15 years.

Eligibility criteria

Study subjects will be low birth weight babies (born before 37 weeks), hospitalized in the neonatal unit of the Laquintinie hospital Douala, Cameroon. The gestational age will be determined either from the mother's last menstrual period, first trimester ultrasound, or physical examination by a pediatrician using the Ballard score.

Exclusion criteria: Low birth weight infants with a birth weight >2500g.

Sampling method

We will use consecutive sampling as we will be examining the medical records of all infants that meet the study criteria. This method of sampling includes all available subjects hence making the sample a better representation of the entire population.

 Data Collection procedure

The protocol will be submitted to the National institutional review board of Cameroon through the institutional review board of the Faculty of Health sciences of the University of Buea for ethics approval. Once the study is approved, a written authorization will be sought from the director of the hospital to enable us carry out the study. Informed consent will not be obtained from the participants as we will be using hospital data.

 We will retrospectively examine the medical reports of all low birth weight (born before 37 weeks) hospitalized in the referral hospital from January 2000 to December 2015. The gestational age will be estimated on the basis of the date of the last normal menstrual period, ultrasonography of the fetus, and physical examination of the neonate by the pediatrician. From these records, we will use a pre-structured case reporting form developed for the study to identify maternal socio-demographic details such as the age, occupation, level of education, multiple pregnancy and pregnancy history, to enable us identify maternal risk factors. Next, we will identify the fetal factors, such as the gestational age, gender, weight, place of birth, apgar, resuscitation and treatment received birth. We will also follow the evolution of these infants while in the unit, to identify major outcomes such as infections, development of other complications of prematurity, other morbidities, and the final outcome upon discharge from the neonatology unit. Hence, this will enable us to identify possible maternal and fetal risk factors for morbidity and mortality in preterm infants. For the sake of this study, the hospital mortality rate will be calculated as the number of low birth infants hospitalized in the Neonatology unit of the hospital who died during hospitalization divided by the total number of low birth weight infants hospitalized during the study period. We will use the Post menstrual age (PMA) at discharge as a marker of length of stay; this is defined as the gestational age at birth plus the length of stay at final discharge from any neonatal unit or death.

Data Management Plan

Data records will be captured manually from physical files into a computer using a pre-structured collection form (adapted from a previous study [32]), following ethics approval and authorization from the director of the study site. All the outcome variables have been listed on the form and codes assigned to them. These will be used to create a data dictionary and a code book.

In the advent of modifications to the protocol due to challenges faced during the study, all modifications will be recorded and reported when presenting our final findings. We will also write to the ethics committee for approval in case of major amendments to the protocol.

Prior to the onset of data extraction we will randomly select 10 medical records on which we will pretest the form. The data collection process will be carried out in an office in the archives unit of the hospital to which entry is strictly on authorization by the principal investigator during working hours. The anonymized data will be captured from the data extraction form into a computer that is protected by passwords. During the study period, data will be shared with the supervisors through emails, and drop box. The information will be backed up drop box, and automatically on Google. We will also save the information in a USB. These measures will prevent the loss or damage of data.

After completing the data extraction process, 10% of the forms will be randomly selected by the supervisor and verified to ensure proper data extraction.

Statistical consideration

We will do consecutive sampling hence include all available medical record. Data will be captured using Excel version 2010 and Stata version 13 for Windows will be used for all analysis. Level of significance will be considered when P value is less than 0.05.

Data Analysis:

The analysis of collected data will be carried out based on our objectives. A data extraction form was designed, with the measured outcomes aimed at attaining each objective.

Objective 1: To describe the demographic and obstetric characteristics of the mothers:

Outcome variables to be measured

   i.   Demographic characteristics: age (Numerical variable)
   We will describe the maternal ages in years, noting the mean age, standard deviation, and the range. Then ages will be divided into subgroups ($\leq$ 20, 21 -25, 26 – 30, >30, unknown) so we can examine in which subgroup the majority of the mothers fall. This information will be represented on tables of maternal characteristics and bar charts.
ii. Obstetrical Characteristics: parity, number of antenatal visits.

   These are numerical variables and we will describe them noting the means and standard deviations, ranges and confidence intervals. We will also be measuring categorical variables such as obstetric complications during pregnancy, obstetric complications during delivery, mode of delivery. The frequency of the various pathologies listed under these outcomes will be calculated. All the results obtained from both the numerical and categorical variables will be represented on a table of obstetrical characteristics and graphically on bar charts

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Objective 2: To describe the characteristics and investigations of the low birth weight infants

Outcome variables to be measured

> i. Clinical conditions of low birth weight infants: Date of birth, Date of admission, place of birth, gender, fetal complications after delivery, apgar, estimated gestational age, birth weight, weight for age, fetal complications present before delivery,
> **Numerical variables**
> The date of birth and date of admission will be used to calculate the delay in hospitalization after birth (Date of admission – date of birth). We will use a weight for age graph, and plot the birth weights against the gestational age to enable us identify infants that were preterm and small for gestational age.

> ii. Investigations: laboratory investigations, radiological investigations

> This is a categorical variable. The frequency of all investigations carried out will be represented on a bar chart

Objective 3: Examine the trend of outcomes (complications of prematurity, mortality) in low birth weight newborns hospitalized in HLD during the study period (MDG period (2000-2015)

Outcome variables to be measured

Complications developed during hospitalization and outcome on discharge are categorical variables. Their frequencies will be calculated and represented on tables and bar charts

Duration of hospitalization (days): This is a numerical variable for which we will find the mean, standard deviation, range and confidence intervals.

Objective 4: Identify factors associated with mortality and morbidity over time.

We will divide the study population into three subgroups based on the category of low birth weight and examine for statistically significant differences of all the outcomes variables in each of these subgroups.

The second division will be based on time. The records examined will be from the year 2001 to the 2015, hence a period of 15 years. We will break this down into three groups of five years (1st January 2001 – December 2005, 1st January 2006 – 31st December 2010, 1st January 2011 – 31st December 2015).

We will test for associations between mortality and each of the outcomes measured in objectives 1, 2 and 3 using the chi-square test for categorical variables and linear regression analysis for numerical normally distributed variables. Multiple imputation method will be used to deal with missing data. Time series analysis will be used to compare the time trends in the outcomes over the three time periods.

Ethical considerations

Independent review**:** Prior to the start of the study we will apply for and obtain approval both from the Ethics committee of Stellenbosch University and the Institutional review board of the FHS of the University of Buea, Cameroon.

Scientific value: Considering the burden of prematurity as evident from the background and rationale, this study is scientifically valid as it will contribute to existing knowledge on the welfare of low birth weight infants.

Scientific validity: The appropriate study design has been chosen for the research and the methodology has been properly planned. We aim at obtaining accurate results at the end of the study by following the steps outlined in the research protocol.

Fair selection of patients: We will carry out consecutive sampling, hence including all available medical records of hospitalized low birth weight infants. Hence all medical records that meet the inclusion will have an equal chance of being included.

Favorable risk/benefit ratio: The risk to the patients is considered minimal as this will be a hospital based study using their anonymized medical hospital records, rendering the information obtained unidentifiable.

Ongoing respect for dignity: Security measures will be taken in the preservation and management of patient data stored in data storage devices. This will be done by encryption and the use of passwords on computers and storage devices containing relevant information.

We will apply for a waiver of consent as we will be doing a record review and no patient contact will be made.

Foreseen Limitations of the study

1. Incomplete/inaccurate medical records
2. Illegible writings in the medical records

Budgeting and Funding

We will be applying for the Harry Crossley grant and the Margaret Mc Namara grant for Africa to enable us cover the expenses of the study

Direct Costs	Budget
Travel expenditures	
Travel to and from Cameroon for the study	R 13000
	R 1800

Daily Transportation to and from study	
Research equipment	
Paper + writing material for data extraction forms	R150
Office supplies: printers + cartridges	R 1000
Calculator	R 50
USB storage device	R 50
Other expenses	
Internet supply, telephone bills	R 400
Total	R 16 450

Motivation of the budget

Travel expenses

A return flight ticket for Cameroon will be purchased after comparing the flight rates of at least three different airlines. We estimate transport to and from the airport to cost about R1000. The air ticket, including taxes and luggage fees is estimated at R12000.

Daily transport fare to and from the study site in Cameroon will be via public transport. A fixed fee of R20 is charged for a round trip. We intend to complete the record review in a period of about 90 days. Hence we budget a total of R1800.

Research Equipment

We will be needing paper for data extraction forms. It is estimated that four reams of paper at R30 will be needed hence a total of R120. We will also need pens and pencils for data collection, estimated at R30. A 4GB USB storage device will be purchased and used to back up data collected for the study in case. We will need a calculator for calculating outcomes such as the duration of hospitalization of the preterm infants from their records. Both the USB storage device and calculator will cost us R50 each.

Printer cartridge for printing and duplication: Printing and duplication will be done using a printer/copier for which a single cartridge costs R1000.00.

Other expenses

Our study site is located out of Stellenbosch University. We have budgeted for internet connection and communication credit as this will enable us stay in communication with supervisors. It was estimated at approximately R160 for 1 GB of data per month for three

months at the standard rate. We also budget R100 for international calls when we need to contact the Stellenbosch based supervisor by telephone.

Timeline and project management

2015								
Milestones	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**
Choosing the research topic	▓							
Developing and writing the protocol		▓	▓					
Peer reviewing and correction of protocol				▓	▓			
Submission for Ethics review and approval						▓	▓	▓
Application for approval from study sites						▓	▓	▓

2016								
	Jan	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**
Collection of data	▓	▓							
Capturing of data			▓						
Cleaning up of data				▓					
Data analysis					▓	▓			
Submission to supervisors for corrections and feedback							▓	▓	
Final submission									▓

The principal investigator will be responsible for the collection and analysis of data under the supervision of the supervisors.

Dissemination of results and Publication Policy

The findings of the study will be translated into both English and French which are the official languages of Cameroon and presented to the personnel of the hospital by scientific presentations during the weekly general rounds held in the hospital every Thursdays.

We intend to work with the staff of the neonatology unit in the hospital to set up a standardized Hospitalization form adapted for low birth weight neonate. This form will be filled for all low birth weight infants upon admission in the hospital and serve as a checklist to guide the staff on all elements required for a proper follow up of these infants. Based on the identified risk

factors, we will work in collaboration with the staff of the neonatology unit to produce a report summarizing possible interventions that could improve the outcome of these preterm infants and submit the report to the Director of the hospital.

We will disseminate the study findings by writing it out as a MSc project that will be submitted to Stellenbosch University. This will be kept in the university library and readily available to other students and researchers doing research in related topics. We hope to have the study published in the journal 'Paediatrics' and presented in several international conferences targeting the welfare of children.

Conflict of Interest

We declare no conflict of interest.

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Data Extraction form

Title :
Study ID number :
Date: --/--/--   **Health Facility**   **Investigator**

A.	Maternal risk factors	
1.	Age (years)	☐ Unknown - 0 ☐ ≤ 20 -1 ☐ 21 -25 - 2 ☐ 26 – 30 -3 ☐ > 30 - 4
2.	Parity	☐ 1 - 1 ☐ 2-4 - 2 ☐ ≥ 5 - 3 ☐ Unknown -0
3.	Antenatal care attendance	☐ No – 0 ☐ Yes – 1
4.	If yes in question 3, how many antenatal visits did the mother attend?	☐ 1 – 1 ☐ 2 - 2 ☐ ≥3 - 3 ☐ Unknown - 0
5.	Obstetric complications during pregnancy	☐ Yes -1 ☐ No - 0
6.	If the answer is yes in question 5 above, which complications did the mother have?	☐ Medical disorder 1 ☐ Hypertensive disorder ☐ Ante
7.	Obstetric complications during delivery	☐ Yes - 1 ☐ No - 0
8.	If the answer is yes in question 7 above, what complications did the mother have?	☐ Extra uterine infections ☐ Intrauterine infections (chorioamnionitis) ☐ Hypertensive disorders ☐ Worsening maternal illness ☐ Maternal Trauma ☐ Poly/oligohydramnios
9.	Placental Complications	☐ No - 0 ☐ Yes - 1 ☐ Unknown - 2
10.	If yes in question 9, which placental complications existed?	☐ Placenta preavia - 1 ☐ Placenta abruption -2 ☐ Others - 3
11.	Number of children (singleton vs multiple pregnancy)	☐ 1 - 1 ☐ 2 - 2 ☐ 3 - 3

B.	Fetal Factors	
1.	Method of delivery	☐ Normal vaginal delivery - 1 ☐ Instrumental delivery - 2 ☐ Ceasarian section - 3 ☐ Unknown - 0
2.	Gender	☐ Male - 1 ☐ Female - 2
3.	Fetal conditions present before delivery	☐ None - 1 ☐ fetal distress ☐ Malpresentation ☐ Malpositioning ☐ Unknown
4.	Fetal conditions present at delivery	☐ Malformations ☐ Cord round the neck
5.	Date of birth	--/ --/ --
6.	Date of admission	--/ --/ --
7.	Was the patient born at LHD	☐ No - 0 ☐ Yes - 1 ☐ Unknown - 2

8.	Apgar at 1 minute	☐ Unknown - 0 ☐ ≤ 3 - 1 ☐ 4-6 - 2 ☐ ≥ 7 - 3
9.	Birth weight (In grams)	
10.	Estimated gestational age (In weeks)	-- weeks
11.	Is the weight appropriate for the estimated gestational age? (weight for age)	☐ Yes ☐ No
12.	Baseline laboratory investigations done (Tick all that apply)	☐ Complete blood count ☐ CRP ☐ CSF analysis ☐ Urine analysis ☐ Haemoculture ☐ Urine culture ☐ Chest xray ☐ Renal function tests ☐ Billirubin levels
13.	Complications developed during hospitalization	
14.	Date of discharge	--/--/--
15.	PMA in days	
16.	Outcome on discharge	☐ Death - 1 ☐ Alive with major complication -2 ☐ Alive and healthy - 3
17.	Duration of hospitalization in days	

Instructions to Authors