Survival of Very Low birth and Extreme Low Birth Weight Infants at Mankweng Neonatal Care Unit

By

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DECLARATION

I declare that this is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

Signature		Date

DEDICATION

In loving memory of my mother Mrs M.D Masete, you were great examples of faith and hard work.

AND

To my father Mr S.D Masete thank you for teaching me discipline and the gift of education you provided for us.

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ABSTRACT

Objectives

To determine the prevalence and survival rate; and to assess the maternal risk factors as well as complications of prematurity, associated with the mortality of very low and extremely low birth weight infants in the Neonatal Intensive Care Unit (NICU) of Mankweng Hospital.

Materials and Methods

A retrospective descriptive study was conducted at the NICU of Mankweng Hospital for a 7-month period from 1st January to 31st July 2015. The patient medical records and the Perinatal Problem Identification Programme (PPIP) data were used for the study.

Results

Prevalence of prematurity was 23%, Infants weighing between 500g-1499g represented 6.3% of the total live births and 25% of the admissions to the NICU; of which 4.9% were classified as extremely low birth weight (ELBW). Overall 77% of the study population survived until discharge. From the medical records, the survival to discharge of infants with weight 500g - 999g was 52%; and 84% for those with weight 1000g-1499g.

Multivariable analysis found that improved survival was associated with an increase in gestational age (p <0.001), as well as birth weight (p <0.001) and prolonged length of stay. Variables associated with poor survival were spontaneous preterm labour (p = 0.031), low Apgar score at 1 and 5 minutes (p <0.001), sepsis (p = 0.001), respiratory distress syndrome (p <0.001), pulmonary hemorrhage (p <0.001), hypothermia (P = 0.005), resuscitation at birth (p = 0.002) and necrotising enterocolitis (p =0.044). Antenatal steroids were not associated with survival (p =0.111), however this was not documented in 53%(134/252) of the records, so the non-significance to outcome in this study may not be a true reflection.

The use of NCPAP or SiPAP only was associated with improved survival of up to 69% and high mortality rates were recorded in babies who required invasive ventilator support. Multi-organ immaturity was found to be the most common cause of death, followed by sepsis.

Conclusion: The prevalence and survival rates of very low and extremely low birth weight, found in this study are comparable to those found in other tertiary hospitals in South Africa. The survival rate of ELBW babies is low and must be improved. Reliable data and further research should address effective steps to prevent preterm labour, extreme prematurity and hypothermia**.** The documentation and provision of antenatal steroids is encouraged.

KEY CONCEPTS: Prematurity, Extremely low and Very low birth weight, Risk factors, Prevalence, Survival, Neonatal mortality rate.

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DEFINITION OF KEY CONCEPTS

Antenatal Steroids: any steroids given to mom with imminent or preterm labour at 26 to <34 weeks gestation, preferably betamethasone 12mg intramuscular injection (IM) repeated after 24 hours or dexamethasone 4mg IM 8hourly for 6 doses, any dose given, course completed or not were grouped together. (National Department of Health, Guidelines for Maternal Care, fourth edition 2015).

APGAR score: a method to quickly summarize the vital or cardiorespiratory function of a newborn infant immediately after birth and response to resuscitation at birth. It is obtained by adding points (2,1, or 0) for the heart rate, respiratory effort, muscle tone, response to stimulation, and skin coloration. The 5-minute score of 7-10 is reassuring, 4-6 is moderately abnormal and 0-3 is regarded as low. In this study the scores were only documented at the 1min and 5 min of life respectively. (American Academy, 2015)

Appropriate for gestational age: birthweight between the 10^{th} and 90^{th} percentile for gestational age

Bronchopulmonary Dysplasia: formerly known as chronic lung disease of the new born, it is the persistent oxygen requirement by 36 weeks postnatal age or at discharge home for infants born <32, and at >28 days but <56 days postnatal age or discharge home if born at ≥32 gestation (Martin et al., 2010)

Ballard Score: a technique used to assess the neurological and physical maturity of the newborn, it assigns a score to various criteria and the sum is then extrapolated to the gestational age, this was done by the admitting paediatrics officer.

Extreme Low Birth Weight: refers to babies born with a birth weight of less than 1000g, regardless of gestational age.

Hypoglycaemia: blood glucose less than 2.6 mmol/l.

Hypothermia: a condition when the core body temperature is less than 36.5°C, it is further categorised as mild (36 to 36.4°C), moderate (32 to 35.9°C) and severe (<32 °C) (Datta et al., 2017).

Intraventricular Haemorrhage: germinal matrix and intraventricular haemorrhage that may extend into the periventricular white matter, diagnosed by ultrasound and graded by the Papile System. (Papile et al., 1978).

Large for gestational age: birthweight above the 90th percentile for babies of the same gestational age

Low Birth Weight: a term used to define babies born with a birth weight of less than 2500g, regardless of their gestational age.

Mothers: each mother was assigned to each neonate; multiple pregnancies were not taken into consideration.

NCPAP: non-invasive respiratory support machine that provides continuous positive airway pressure ventilation via the nose.

neonatal death: deaths among live births during the first 28 completed days of life, which can be further sub-divided into early neonatal deaths (within 0-7 completed days after birth) and late neonatal deaths thus after 7-28 completed days after birth (WHO, 2014).

Necrotising Enterocolitis: ischaemic necrosis of the intestinal mucosa, which is associated with inflammation, invasion of enteric gas forming organisms and

dissection of gas into the muscularis and portal venous system. In this study it was defined according to the radiological and clinical modified Bell's Stage 2 or 3.

Neonatal jaundice: yellow discolouration of the skin and mucous membranes due to hyperbilirubinemia. It is considered pathological if it occurs within the first 24 hours of birth and prolonged when it persists for more than 10 days in the full-term infant or 14 days in the pre-term infant.

Neonate: an infant from birth to 28 days (first four weeks after birth).

Out born: included babies born at another hospital and before arrival at Mankweng Hospital.

Patent Ductus Arteriosus: failure of the ductus to close within 72 hours of life, based on echocardiogram.

Pregnancy Hypertensive Disorders: includes chronic or pregnancy-induced hypertension, and imminent pre-eclampsia and eclampsia.

Pneumonia: infection in one or both lungs

Pulmonary Haemorrhage: acute bleeding from the lungs, especially in the upper respiratory tract and the trachea.

Respiratory Distress Syndrome: a condition in newborn babies in which the lungs are deficient of surfactant, this causes the formation of hyaline material and prevents the proper expansion of the lungs.

Retinopathy of Prematurity (ROP): defined as the disease that affects immature vasculature in the eyes of the premature infants. It can be mild with no visual defects or aggressive with the formation of new blood vessels and can progress to retinal

detachment and blindness. The condition was diagnosed by the attending ophthalmologist as per the international classification of ROP.

Resuscitation: is to revive from apparent death or from unconsciousness. In this study this it meant the need for either bag and mask or NeoPuff (T-Piece), chest compressions, or intubation and ventilation immediately after birth. In this study only, resuscitation at birth was regarded

Sepsis: the presence of bacteria or other infectious organisms; or toxins created by infectious organisms in the bloodstream which spread throughout the body. In this study sepsis was classified as either suspected or culture proven, early (occur in the first 7 days of life or 72 hours of life in the case of VLBW infants) or late sepsis (occur between 7-28 days of life) (Cortese et al., 2015).

SiPAP: a non-invasive respiratory support machine that provides bi-level nasal continuous positive airway pressure (PEEP) as well as an additional synchronised positive airway pressure through the delivery of a sigh to the patient without the need for intubation.

Small for gestational age: birthweight below the 10^{th} percentile for babies of the same gestational age

Surfactant: a surface-active lipoprotein substance secreted naturally in the lungs, a lack of which causes respiratory distress syndrome, especially in premature babies. “Prophylactic treatment” is defined as surfactant given down an endotracheal tube at initial resuscitation. “Rescue treatment” is when the surfactant given to an intubated baby several hours after birth when RDS has been diagnosed.

Survivors: included local neonates who reached the discharge goal weight of 1800g and those who were stable and transferred back to local hospitals, despite their weight being below 1800g at discharge.

Very Low Birth Weight: refers to babies born with a birth weight of less than 1500g, regardless of their gestational age.

ABBREVIATIONS

APGAR: **(A**ppearance, **P**ulse, Grimace**, A**ctivity, **R**espiration)

AGA: Appropriate for Gestational Age

BPD: Bronchopulmonary dysplasia

ARVS: Antiretrovirals

BW: Birthweight

CS: Caesarean Section

ELBW: Extremely Low Birth Weight

GA: Gestational Age

HBB: Helping Baby Breathe

HIV: Human Immunodeficiency Virus

InSurE: Intubation-SURfactant-Extubation

IUGR: Intrauterine Growth Restriction

LGA: Large for Gestational Age

LBW: Low Birth Weight

NCPAP: Nasal Continuous Positive Airway Pressure

NEC: Necrotising Enterocolitis

NNJ: Neonatal jaundice

PDA: Patent ductus arteriosus

PPIP: Perinatal Problem Identification Programme

RDS: Respiratory Distress Syndrome

ROP: Retinopathy of Prematurity

RPR: Rapid Plasma Reagent

SGA: Small for Gestational Age

SiPAP: Synchronised inspiratory Positive Airway Pressure

UNICEF: United Nations International Children's Emergency Fund

VLBW: Very Low Birth Weight

WHO: World Health Organisation

CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 Introduction

This study sought to determine the survival of very low and extremely low birth weight infants of 500g-1499g admitted to the Mankweng Hospital Neonatal Care Unit, a tertiary hospital in the Limpopo Province with limited resources. This chapter presents background information, the problem statement, significance, research questions, aims and objectives of the study.

1.2 Background of the study

Prematurity continues to be a public health problem worldwide. The rate of prematurity is relatively high in low and middle-income countries, particularly in Sub-Saharan Africa and South Asia (WHO, 2013). In South Africa, a study undertaken at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) showed an increase of 18.5 % of VLBW admissions in 2013 compared with 2006/2007 (Ballot et al., 2015). The economic impact of preterm birth in terms of immediate neonatal intensive care, ongoing long term complex health needs, as well as lost economic productivity is profound (Blencowe et al., 2013).

For the past two decades improved survival to discharge has been documented in developed countries. This is attributed to improved prenatal and neonatal care (Rocio et al., 2014; Kalimba et al., 2013). Survivors, however, have increased long

term sequelae, such as increased death in the 1st year of life, neuro-developmental and specific physical effects, compared to full term babies. This exerts a heavy burden on families, society, and the health system (Blencowe et al., 2013, & Watkins et al., 2016).

In South Africa a handful of studies on the survival of preterm babies were documented. A study done at CMJAH showed improved survival rates of especially neonates with weight of 750-900g at birth, most likely due to the provision of surfactant and NCPAP, however, survival of these infants is still very low (Ballot et al, 2015).

1.3 Problem Statement

Neonatal mortality is a significant contributor to the under 5 mortality rate (U5MR). Most neonatal deaths are secondary to immaturity (WHO, 2015). Health intervention programmes must be based on reliable statistics applicable to the local setting; however, this is the first study on the prevalence and survival of premature babies at Mankweng Hospital, the only tertiary hospital in the predominantly rural province of Limpopo.

1.4 Significance of the study

The South African U5MR remains high, at 37 per 1000 live births (MRC, 2015) and neonatal mortality contributes up to 45% of the mortality globally (WHO, 2015). In this country, similar studies were done in other centres but never at this institution.

An audit of disease and mortality patterns provides essential information for health budgeting and planning; and intervention programmes must be based on reliable statistics applicable to the local setting. This study will provide reliable, recent statistics relevant to the Limpopo Province, useful for guiding neonatal interventions in the local setting.

1.5 Research Questions

- What is the prevalence and survival rate of neonates with birth weight between 500g–1499g?
- What are the associated maternal risk factors that contribute to premature birth?
- What are the complications of prematurity associated with their mortality, at Mankweng Hospital, a tertiary institution in the Limpopo Province?

1.6 Aim

The aim of this study is to report on the neonatal survival rate of very low and extremely low birth weight infants at the Mankweng Hospital Neonatal Care Unit.

1.7 Objectives of the study

- To determine the prevalence rate of very low and extremely low birth weight neonates;
- To determine the survival rate of very low and extremely low birth weight neonates;

- To determine the maternal risk factors as well as complications of prematurity, associated with their survival and mortality at Mankweng Hospital.

1.8 Conclusion

Prematurity continues to be a public health problem worldwide, especially in low and middle-income countries, particularly in Sub-Saharan Africa and South Asia (WHO, 2013). This study will provide reliable, recent statistics relevant to the Limpopo Province, useful for guiding neonatal interventions in the local setting. Details about the research methodology will be discussed in Chapter 3.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter discusses the literature reviewed on the survival of very low and extremely low birth weight infants.

Preterm birth is defined by World Health Organisation(WHO) as all live births before 37 completed weeks of gestation or fewer than 259 days since the first day of a woman's last menstrual period. It can be classified based on the gestation from a combination of maternal history to include the expected date of delivery, height of fundus, first trimester ultrasound and the Ballard score.

It can be further sub-divided based on gestational age: extremely preterm (<28 weeks), very preterm (28-32 weeks) and moderate to late preterm (32-37 weeks) (Blencowe et al., 2013). However, maternal history is not always accurate and use of the Ballard Score Card by experienced health care practitioners is more accurate but can vary by two weeks above or below the true gestation. Another classification used is based on the weight of the neonate, thus low birth weight is birth weight <2500g, very low birth weight is birth weight <1500g and extremely low birth weight is birth weight <1000g (WHO, 2013).This classification further categorises babies into appropriate for gestational age (AGA), small for gestational age (SGA) or large for gestational age (LGA) (WHO, 2013).

2.2 Background

An estimated 18 million babies are born prematurely globally every year (representing 14% of all births) and the number is rising. Over 60% of these cases occur in Sub-Saharan Africa and South Asia and annually over 4 million of these babies die before one month of age due to complications of immaturity (WHO, 2013, Blencowe et al., 2012). More than 1 in 10 babies are born preterm globally and immaturity is the leading contributor to the death rate of under 5 years of age after pneumonia (WHO, 2015). It is estimated that in South Africa 8 out of a l0 infants are born prematurely annually (WHO, 2015).

Studies done in USA and Europe, have documented prevalence rate of VLBW at 3.4% and 1% of all live births, respectively (Numerato et al., 2015). Cardoso and colleagues, in their study conducted in Brazil, reported that 1.2% of the total live births were VLBW (Cardoso et al., 2013). In Africa, reports from Gabon, Togo and Cameroon indicate that the rate of prematurity can vary from 11.1% to 57% (Chiabi et al.,2013). In South Africa, Kirsten et al found that rate of prematurity is 22% and VLBW contributes 4 -5% of the total births (Kirsten et al., 2012). A study at Chris Hani Baragwanath Hospital (CHBH) found that VLBW represented 3% of the total live births and 21% of the admissions (Velaphi et al., 2005). In a study done at Steve Biko Academic Hospital (SBAH) Lloyd et al., found that 8.3% of neonatal admissions were classified as ELBW and 23.6% as VLBW (Lloyd et al., 2013). In another study at Madedeni, a regional hospital in Kwazulu-Natal South Africa, VLBW represented 3.7% of the total admissions, 24% were ELBW and 76% 1000g-1499g (Bondi et al.,2007).

South Africa is one of the many Sub-Saharan African countries which did not meet its Millennium Development Goal 4, which was to reduce the mortality rate of children under the age 5 years (U5MR) by two-thirds between the year 1990 and 2015. The target rate was 20 per 1000 live births. The U5MR reflects the number of children under five years who die in a year per 1000 live births during the same year. UNICEF uses the U5MR as the principle indicator of human and economic progress (Kibel et al., 2012). Although substantial improvement was achieved, much remains to be done. South Africa's U5MR is documented as 37 per 1000 live births, according to the Medical Research Council (Global Burden of Disease Study, 2015)). Lessons learned from the MDG 1990-2015 can be used to help achieve the Sustainable Development Goals (SDG).

The Sustainable Development Summit was held in New York, USA, from the 25th to the 27th of September 2015, leading to the adoption of the Sustainable Development Goals (SDG) by the UN general assembly, with South Africa included. The SDG target number 3.2 aims to end preventable deaths of newborns and children under 5 years of age, by reducing the neonatal mortality rate of all countries to 12 or less per 1000 live births and U5MR of at least 25 per 1000 live births by 2030 (Murray et al., 2015).

Globally, as well as in South Africa, neonatal deaths accounts for between 40-45% of the deaths of children under the age of 5 years (WHO, 2015; Lawn et al., 2005). However, generally speaking, as the U5MR decreases, the perinatal conditions, especially prematurity, continue to contribute to a higher proportion of the deaths under 5 years of age. Therefore, it is important to know the associated perinatal and

neonatal risk factors to undertake proper intervention strategies, which could significantly decrease the neonatal deaths. This is especially true regarding strategies like the use of antenatal steroids and nasal CPAP; and the provision of surfactant, since studies have shown that these interventions have a major impact in reducing neonatal mortality (Ballot et al., 2015; Lloyd et al., 2013).

Prematurity is an explicit public health priority in many high-income countries (Howson et al., 2013) and is a national health priority in South Africa. The National Department of Health (NDOH) and Child Health Cluster has developed a national plan. The plan's priority actions are focused on newborn and maternal care for the country as recommended by the National Perinatal Mortality and Morbidity Committee (NAPEMMCO) 2013 report.

The NAPEMMCO report makes use of the Perinatal Programme Identification Programme (PPIP), a South African national tool for perinatal death audit since 1999. The report was compiled using information gathered from different sites in the country, as well as information from the Saving Babies Report, to give insight into the quality of care rendered in the South African health care system. It is summarised as the "HHAPI-NESS road map for healthy babies in South Africa". The recommendations contained in the report include plans to improve the (H)health system for mothers and babies; (H)improve the knowledge and skills of health care providers in maternal and neonatal care; (A)reduce deaths due to asphyxia; (P)reduce death due to prematurity and (I)reduce deaths due to infection, this is incorporated in the (N)Neonatal (S)Survival (S)Strategy (National Department of Health of South Africa, 2013).

Social and economic inequalities were noted to be associated with increased risk of preterm birth, even in developed countries, with early (<32 weeks) preterm birth rate twice as high in those who were poor and had lower education levels (Heather et al., 2016). In addition, studies have found that poverty contributes to a higher prematurity rate, with mothers from poor families being at high risk of premature birth (Cardoso et al., 2013; WHO, 2015).

In a study done at Tygerburg, a tertiary hospital in South Africa, obstetric risk factors leading to preterm birth were hypertension, preterm labour and prelabour rupture of membranes in VLBW babies ((Odendal et al, 2003). Robert and co-workers found that 30-35% of preterm births were for maternal or foetal indications, 40-45% followed spontaneous preterm labour and 25-30% followed preterm premature rupture of membranes (Robert et al., 2008).

2.3 Outcome of Low Birth Weight Infants

The neonatal mortality rate is defined as the number of neonatal deaths (during the first 28 days of life) per 1000 live births. It is a key outcome indicator for newborn care and directly reflects on the prenatal, intrapartum, and neonatal care accessed (WHO, 2013). It is estimated that, globally, the neonatal mortality rate decreased from 33.2 to 23.9 per 1000 live births between 1990 and 2009; a reduction of 28% or 1.7% per year. However, low income countries showed a lower reduction of 17% compared with 40% in high income countries (Lawn et al., 2005). The South African neonatal mortality rate, according to Statistics South Africa, 2015, is 12 per 1000 live

births compared to 3-5 per 1000 live births in the developed countries, which is attributed to the improved human and physical resources in those countries (Lawn et al., 2005; Velaphi et al., 2012).

In the past 20 years, developed countries have reported an improved survival rate of particularly ELBW babies, with a survival rate of >90% compared to <10% in some developing countries, owing to interventions such as antenatal steroid therapy, timely caesarean section deliveries, good resuscitation techniques, surfactant therapy, the use of expensive technology like NCPAP/SiPAP and invasive mechanical ventilation (Tagare et al., 2013; WHO, 2015). However, availability of these resources is limited in developing countries like South Africa (Lawn et al., 2005), especially for the treatment of extremely low birth weight infants. In high income countries, 9/10 preterm babies have access to these interventions as compared to 1/10 in low income countries (WHO, 2015). However, low cost methods like bubble CPAP have also been shown to improve survival of premature infants and equipment does not have to be expensive (Bateman et al., 2013).

Helping Babies Breathe (HBB) is an evidence-based educational program in neonatal resuscitation techniques in resource limited areas. This is an initiative of the American Academy of Paediatrics, in collaboration with WHO and several other global health stakeholders. Training all birth attendants in skills-based neonatal resuscitation may reduce deaths of full-term babies by up to 30% and reduce by 5-10% the neonatal deaths due to prematurity (American Heart Association., 2015). In Tanzania, the introduction of HBB was associated with a 47% reduction in all-cause newborn mortality in the first 24 hours (Arlington et al., 2017).

Ballot and co-workers found that survival in neonates who weighed 750-900g significantly improved from 20% in 2006/2007 to 52% in 2013(p=0.001), due to provision of surfactant and NCPAP (Ballot et al.,2015). In a study done at Tygerberg Children's hospital, use of NCPAP, InSurE and use of maternal antenatal steroid contributed significantly to the survival ELBW infants until discharge(p=0.0017), with 80% survival of infants who required NCPAP only and 67% survival of those who required InSurE only (Kirstein et al., 2012).

Survival of these infants is documented to vary from country to country as well as hospital to hospital, depending on the quality of antenatal, intrapartum, and neonatal care. Therefore, it is important that health care providers at obstetrics and neonatal units know the outcomes of these infants in their own hospitals (Velaphi et al., 2005; Rajin et al., 2011).

In India, the rate of survival of very low birth weight infants was 63% (Basu et al., 2008); 74.5% in Turkey (Canbak et al., 2011); 85% in the USA (Horbar et al., 2012) and 63.4% in Cameroon (Chiabi et al.,2013). In South Africa, a study done at the Chris Hani Baragwanath Academic Hospital (CHBAH), the survival rate for infants with birth weight (BW) 500g -1000g was 32% and 84% for those with BW of 1000g-1500g (Velaphi et al., 2005). Survival at Madeni hospital for infants with BW 1000g-1499g was 36% and 5% for those with weight 500g-1000g. Studies at CMJAH showed that the survival rate of infants ≤ 900g was 26.5% and 34.9% for <1001g, 86% of infants with birth weight 1001- 1500g, overall survival of VLBW was 73.4% (Kalimba et al., 2013; Ballot et al., 2010; Ballot et al., 2015).

Many studies mentioned that prematurity occurs more often in male infants and that male infants are more likely to die compared to the female infants (Blencowe et al., 2013; YI-YU Su et al., 2016). Ballot found that NEC and hypotension were significantly related to mortality (Ballot et al., 2010). In two studies done at CMJAH the most common cause of death in both studies was extreme multi-organ immaturity. (Kalimba et al., 2013; Ballot et al., 2015). Velaphi and co-workers found that the most common cause of death was related to prematurity followed by sepsis (Velaphi et al., 2005). Bondi found that respiratory distress syndrome, immaturity, NEC and intraventricular haemorrhage were the commonest causes of death (Bondi et al.,2007)

Furthermore, infants who survive have higher rates of increased mortality in the first year of life, with death rate up to 130 times more likely in the weight range 500g-1499g than babies weighing >2500g (Watkins et al., 2016). Blencowe and co-workers found that, in addition to the high mortality, there are life long-term complications amongst survivors, such as impaired neuro-developmental functioning, increased risk for cerebral palsy, learning impairment and visual disorders, as well as affecting long term physical health, with a higher risk of contracting a non-communicable disease and this exerts a heavy burden on families, society, and health system (Blencowe et al., 2013).

2.4 Conclusion

Prematurity is a serious public health problem globally and especially in developing countries like S.A. It contributes to the high U5MR and furthermore survivors have

life long-term complications throughout life such as impaired neuro-developmental function, increased risk for cerebral palsy, learning and visual impairment, as well as long term physical health with a higher risk of non-communicable disease, and this exerts a heavy burden on families, society. Therefore, this study sought to find the maternal factors that contribute to prematurity, the neonatal complications, the causes of death and survival rates of VLBW and ELBW infants admitted to a tertiary centre with limited resources, to improve care and survival of these infants. The next chapter will discuss the research methodology used in the study.

CHAPTER 3

METHODOLOGY OF THE STUDY

3.1 Introduction

In this chapter, the methodology used in this study is discussed. The chapter describes the research design, the study setting, the population under study, sample size and sampling technique and the procedure used for data collection and data analysis. The measures taken to ensure reliability and validity of the research instrument are also addressed. Lastly, ethical considerations pertaining to the research are discussed.

3.2 Study design

This study was conducted in two phases. To avoid inadequate sampling of the study, data for both phases were collected over a 7-month period, from 1st January to 31st July 2015, from the Mankweng Hospital Neonatal Care Unit. This data included all infants with the birth weight of 500g-1499g. The first phase of the study involved a retrospective review of the existing Mankweng Neonatal PPIP computer database, which was used to determine the prevalence and survival rate; and to classify the causes of death. The second phase involved a retrospective review of the retrieved neonatal records identified from the neonatal admission register. The data collected was used to determine the maternal and neonatal risk factors associated with survival and mortality.

3.3 Study site

The study was conducted at the Mankweng Hospital, a tertiary hospital in the Limpopo Province of South Africa. The hospital is the main referral centre for high risk pregnancies and neonates who require intensive care from all district and regional hospitals in Limpopo and from the surrounding local clinics. The neonatal intensive care unit is a sixty-bed unit; with nine beds reserved for intensive care and nine reserved for high care, as well as a nursery with thirty beds and twelve Kangaroo Mother Care (KMC) beds.

3.4 Study population

In this study, the study population included all neonates admitted to the Mankweng Neonatal Care Unit with weight between 500g -1499g (twins were analysed separately).

3.5 Protocol for Treatment

Due to limited resources in the Neonatal Care Unit of this hospital (i.e. beds and mechanical ventilators), infants <1000g with respiratory distress are not put on mechanical ventilation but are put on supplemental oxygen via low-flow nasal cannula (NPO2), and either SiPAP or NCPAP. Surfactant is given to infants with BW > 800g or ≥26 weeks, requires > 40% FiO2 on NCPAP/SiPAP, as a rescue treatment rather than prophylaxis, however at the discretion of the consultant e.g. a mother with a bad obstetric history, infants with BW< 800g and ≤26 weeks may be given

surfactant. Otherwise, all infants are given the same neonatal care regarding resuscitation, warmth, intravenous antibiotics, supplemental oxygen and phototherapy.

At the time of the study the unit was run by one neonatologist from Europe, a general paediatrician, and registrars. Echocardiography was mostly done as an emergency during the time of the study as there was only one echocardiography-trained general paediatrician covering the entire Limpopo Province. Cranial ultrasound was only done per availability of the sonographer and if intraventricular haemorrhage was clinically suspected.

All babies with birth weight of <1500g or <32 weeks gestational age are eligible for ROP screen within 4 -6 weeks chronological age. According to the KMC admission protocol, only infants with weight 1000g-1799g; who maintain saturation on room air; who are off antibiotics; and can cup feed and tolerate full feeds, are eligible for KMC. The discharge to home weight of babies is 1800g. Infants who are stable and not from the local area are transferred to their local hospitals for KMC before reaching a weight of 1800g.

3.6 Sample Size and Sampling Technique

Time and money was saved by selecting a sample to be studied rather than attempting to study the entire population of ELBW and VLBW admitted to the Mankweng Hospital.

Sample for phase one: The PPIP database was reviewed and a consecutive sample (all admissions and deaths) of neonates weighing 500g-1499g were included in the study.

Sample for phase two: A sample size of 185 was requested for the study. The sample size calculated based on the formula below: All consecutive neonates recorded in the admission register with a weight of 500g-1499g during the period of the study were selected.

$$n = \frac{Z^2 p(1-p)}{e^2} = \frac{(1.96)^2 0.14(0.86)}{(0.05)^2} = 185$$

Where

n= sample size

Z ~ 95% confidence interval

p ~ prevalence of low birth weight babies (p=14%, lawn et al., 2005)

e ~sampling error (5%)

3.7 Inclusion and Exclusion Criteria

3.7.1 Inclusion criteria

All neonatal infants admitted to the Mankweng Neonatal Care Unit with birth weight of 500g-1499g during the study period were included.

3.7.2 Exclusion criteria

The following neonates were excluded from the study:

- All records of neonates who were admitted in the unit as a referral after 24 hrs of birth;
- Babies who died in the delivery room;
- Those babies with other congenital heart diseases, except Patent Ductus Arteriosus, based on cardiac echocardiography; and
- Neonates with severe congenital anomalies trisomy 13, 18, 21 and other multiple congenital defects.

3.8 Data Collection Tool

A data collection tool was developed, comprising of two sections. Section A: included information on the demographic characteristics of the mother, which included the following variables: Age, Parity and Gravidity, HIV and RPR status(treated or not), obstetric diagnosis (including: Spontaneous preterm labour, Obstetric hemorrhage, Pregnancy induced hypertensive disorders, Abruptio placenta, Preterm rupture of membranes, Placenta praevia and other), Mode of delivery and whether she received Antenatal steroids or not (course completed or incomplete, grouped together).

Section B: included information on the demographic characteristics of the infant, which included the following variables: Birth weight(BW), Gender, Gestational age (GA), Referred or Inborn at Mankweng, APGAR score, Resuscitation at birth,

Complications during hospital stay (including: RDS, Pulmonary hemorrhage, Pneumonia, Bronchopulmonary dysplasia (BPD), Hypothermia, Hypoglycaemia, Neonatal jaundice, Necrotising enterocolitis (NEC), Retinopathy Of Prematurity (ROP), Intraventricular hemorrhage (IVH) and Patent Ductus Arteriosus (PDA), and Interventions (including: Surfactant, either NCPAP or SiPAP and Mechanical ventilation), as well as Outcome (died/discharged home or to the local hospital) and cause of death, if the infant died.

The Perinatal Problem Identification Programme (PPIP) classification data for Mankweng Hospital over the same period was reviewed to establish the main cause of death.

3.9 Data Collection

For phase one, the PPIP database over the same period was reviewed, while for phase two the medical records of neonates with birth weight of 500g-1499g was retrieved and reviewed. The PPIP database review and analysis was performed by the researcher with the help of the statistician and Provincial Child and Nursing Health Coordinator, while data collection for phase two was performed by the researcher.

3.10 Data Analysis

Data was analyzed using STATA version 10 (StataCorp 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorpLP). Frequency tabulations

and percentages for categorical data and for continuous data, summary measures such as mean and standard deviation (SD) were used to interpret the data. The associations between neonatal outcome and demographics and clinical characteristics were investigated using the Chi-squared test. P-value <0.05 was considered statistically significant.

3.11 Reliability, Validity, Objectivity

The instrument was piloted and changed accordingly.

3.12 Bias

To avoid selection bias, consecutive files of neonates weighing 500g-1499g were retrieved and reviewed over the 7-month period of the study.

3.13 Ethical consideration

3.13.1 Permission

Ethical approval for the study was granted by the Turfloop Research Committee, project number TREC/84/2016 and permission to conduct the study was also granted by the Limpopo Department of Health. The following principles were considered for this study:

3.13.2 Informed consent

Consent from parent(s) was not required as this was a retrospective study of the neonatal records and the PPIP data.

3.13.3 Confidentiality

All the medical records were consulted in the neonatal unit and each file was given an anonymous number 1 - 252. No names or hospital numbers were used to ensure confidentiality.

3.13.4 Harm

Physical, social, legal and financial harm were avoided by protecting the patient's anonymity and confidentiality.

3.14 Conclusion

In this chapter, the materials and methods used for the study were presented. In Chapter 4, the results of the study are presented and interpreted.

CHAPTER 4

PRESENTATION AND INTERPRETATION OF THE FINDINGS

4.1 Introduction

In the previous chapter, the methodology used for the study was presented. In this chapter, the study findings are presented and interpreted. The chapter is subdivided into: (1) prevalence rate of very and extremely low birth weight neonates, (2) demographic characteristics of the neonates and the mother, (3) survival rate and risk factors associated with ELBW and VLBW infant survival and (4) the causes of deaths for very and extremely low birth weight infants.

4.2 Prevalence rate of VLBW and ELBW infants

According to the Mankweng PPIP data (Table1), there were 3793 births over the 7-month period of the study. Of these, 97% (3667/3793) were born alive and 3%(114/3793) were stillbirths, which were excluded from this study. Among the 3667 live births, 6.3% (231/3667) were VLBW; of these (n=231), 75% (n=173) weighed between 1000g–1499g; and 25% (n=58) were <1000g (ELBW) and were eligible for this study.

The hospital records report that, 34.7 %(1273/3667) of the live births were admitted to the neonatal unit during the period of the study. Among the 1273 admissions, 25% (n=318) were VLBW, of which 80% (n=256) were of birthweight 1000-1499g and 20% (n=62) were ELBW. Among these VLBW (n = 318), medical records of 84.5% (269/318) were retrieved, the rest could not be found. Overall, 17 neonatal records

were excluded, of these 3 had no neonatal data, 12 were admitted after 24 hrs of birth as referrals, 2 files had diagnosis of trisomy 18 and the other of multiple congenital abnormalities. Therefore only 252 neonatal records met the inclusion criteria and were enrolled in these study, each mother was assigned to each neonate; multiple pregnancies were not taken into consideration.

Since this is retrospective study, therefore more likely to have missing data, 21 more infants were retrieved from the medical records (table 4) compared to the PPIP data (table 1). Of the infants with BW 500g -999g there was 8 more infants from the PPIP data vs the medical records and 29 more infants with BW 1000g-1499g were retrieved from the medical records, this may be the infants who died shortly after birth in labour ward or theater and were therefore excluded as per protocol of this study, it may also be infants with trisomy 13/18/21 and other multiple congenital defects which were excluded in this study or live discharges/transfers that are not captured on the PPIP data.

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Table 1: PPIP Data of infants born at Mankweng Hospital from 1st January to 31st July 2015

Birth weight	Born alive n=3667(%)	Survived n=3542(%)	Non-survivors n=125(%)	p-value
500-999 g	58(1.6)	17(29)	41(71)	<0.001
1000-1499g	173(4.7)	139(80)	34(20)	<0.001
1500-1999g	229(6.2)	208(91)	21(9)	<0.001
2000-2499g	377(10.3)	365(97)	12(3)	<0.001
≥2500g	2830(77.8)	2813(99)	17(1)	<0.001

4.3 Demographic Characteristics of the Study population

4.3.1 Neonatal characteristics

The demographics characteristics of the infant are shown in Table 2. Most (59%) of the infants were female, with mean GA of 31±2.5 weeks. The mean GA was 31 (±2.5), and majority 65%(165/252) of the infants were of 30-34 weeks gestational age. The mean BW was 1180±206g, with a range from 610g to 1495g. Eighty per cent of infants were 1000g-1499g followed by those with BW of 750-999g (16%) and <750g (4%).

Eighty-five per cent (213/252) of the infants were inborn with the rest either referred from the district and regional hospitals, surrounding local clinics or or born before arrival (BBA). The mean APGAR scores at 1 and 5 minutes was 6.7±1.8 and 8.8±1.3, respectively. Thirteen per cent of the babies required resuscitation at birth. The mean length of stay was 17.4±16.3 days with 49% (124/252) staying for 8-28 days

Table 2: Infant demographics of the study population

	n	%
Infant gender		
Female	150	59
Male	102	41
Gestational Age	31±2.5	
<28 weeks	25	10
28-29 weeks	38	15
30-34 weeks	165	65
35-36 weeks	24	10
Place of delivery		
In-born	213	85
Out-born	39	15
Birth weight	1180±206	Range:610-1495
<750	9	4
750-999	41	16
1000-1499	202	80
Apgar scores (/10)		
1 min	6.7±1.8	
5 min	8.8±1.3	
Resuscitation at birth	32	13
Length of stay (days)	17.4±16.3	
≤7	81	32
8-28	124	49
>28	47	19

4.3.2 Maternal characteristics

Overall 252 mothers paired with a child were included in this study. The mean maternal age was 26.4±6.6, majority 69%(174/252) of the mothers were in the age group 20-34 years. The mean parity was 1.0±1.21 and 36%% (90/252) were primigravida versus 54% multi parous, 11%(27/252) parity was not recorded. only 1% of the mothers were RPR positive and were treated, a small number 4% (10/252) were not recorded. The majority 79% (200/252) of the mothers tested HIV negative, 19%(48/252) tested positive and 85%(41/48) were on ARV's, 2%(4/252) HIV status was were not recorded.

Table 3: Maternal demographics of the study population

	No (252)	%
Maternal age (years)	26.4±6.6	
<20	33	13
20-34	174	69
35+	43	17
Not recorded	2	1
Parity	1.0±1.21	
0	90	36
1-3	124	49
>3	11	4
Not recorded	27	11
RPR		
Negative	241	95
Positive	1	1
Not recorded	10	4
Treated: Yes	1	100
No	-	-
HIV status		
Negative	200	79
Positive	48	19
Not recorded	4	2
Treated: Yes	7	15
No	41	85
ANC Steroids		
No	16	6
Yes	102	40
Not recorded	134	53
500-999g	27	20
1000-1499g	107	80
Mode of delivery		
CS	139	55
Normal	113	45

Although 40% of the mothers received ante-natal steroids, a large number 54% (134/252) had no record of ante-natal steroids, of theses 20%(27/134) gave birth to ELBW and 80%(107/134) VLBW infants. According to the hospital obstetrics protocol, all mothers admitted at 26 to 33 weeks gestation or an estimated foetal weight of 800g to 1999g if gestation is unknown are to be given antenatal steroids (Guidelines for Maternity Care in South Africa, 2015), protocols may not be always followed, especially if mothers arrive fully dilated etc, data on antenatal steroids was

not documented in most files. Fifty-five per cent (139/252) of these mothers delivered via caesarean section (CS), indications for CS were not recorded in most cases.

4.4 Risk factors associated with ELBW and VLBW infant survival

4.4.1 Infant characteristics as risk factors for neonatal mortality

The gender (p = 0.554) and place of delivery (p = 0.364) were not associated with poor outcome. Survival increased with the G.A (p<0.001), with a high mortality of 65%(16/252) vs 36%(9/252) survival of infants <28 weeks.

Survival to hospital discharge improved with increase in BW (p<0.001) according to the neonatal records data, with a significant increase rate of survival from 33%(3/9) to 56%(23/41) of babies with BW<750g and 750g- 999g amongst the ELBW respectively. Infant weighing 600-799 (OR 10.9; 95%CI:3.6 - 32.9; p<0.001) and 800-899 (OR 11.8; 95%CI: 3.6 - 38.4; p<0.001) were more likely to die compared to those with BW 1100g-1499g. In Table 5, on logistic regression of infant outcome and birth weight, there was a marked improved survival from BW 900g-999g (OR 2.1;95%CI: 0.7 - 6.5; p=0.164) compared to infants with BW 1100g-1499g. There was significant improved survival of infants from BW 1000g-1099g (OR 3.61;95%CI:4 - 8.8; p=0.04), probably because infants ≥1000g were legible for ventilation. According to the medical records data majority 87%(169/195) of the survivors were those with BW of 1000g -1499g vs 13%(26/195) of ELBW, overall 16%(33/202) of the infants with BW 1000g- 1499g versus 48% (24/50) of the ELBW infants died, Eighty per cent (139/173) of the infants with BW 1000g-1499g survived versus 29%(17/58) of the ELBW according to the PPIP data.

Table 4: Infant characteristics as risk factors for neonatal mortality

	n=252 n (%)	Survivors n=195 (%)	Non-survivors n=57 (%)	p-values
Infant gender				
Female	150(59)	118(79)	32(21)	0.554
Male	102(41)	77(75)	25(25)	
Gestational Age	31±2.5	31 ±2.3	29±2.6	<0.001
<28 weeks	25(10)	9(36)	16(64)	<0.001
28-29 weeks	38(15)	26(68)	12(32)	
30-34 weeks	165(65)	137(83)	28(17)	
35-36 weeks	24(10)	23(96)	1(4)	
Place of delivery				
In-born	213(85)	167(78)	46(12)	0.364
Out-born	39(15)	28(72)	11(28)	
Birth weight	1180±206	1224±180	1030±221	<0.001
<750	9(4)	3(33)	6(67)	<0.001
750-999	41(16)	23(56)	18(44)	
1000-1499	202(80)	169(84)	33(16)	
Apgar scores (/10)				
1 min	6.7±1.8	7.0±1.7	5.8±1.9	<0.001
5 min	8.8±1.3	9.1±1.1	8.0±1.5	<0.001
Resuscitated	32(13)	18(9)	14(25)	<0.002
Length of stay (days)	17.4±16.3	20.3±16.0	7.4±13.4	<0.001
≤7	81(32)	48(59)	33(41)	<0.001
8-28	124(49)	104(84)	20(16)	
>28	47(19)	43(91)	4(9)	

The mean Apgar scores at 1min for survivors was higher 7.0±1.7 compared to 5.8±1.9 for non-survivors (p <0.001). Thirteen per cent (32/252) of the infants admitted required resuscitation, 56%(18/32) vs 44%(14/32) survived, proportionally 25%(14/57) of the non-survivor's vs 9%(18/195) were resuscitated on admission and this was statistically significant (p <0.002). Average length of stay for survivors was longer at 20.3±16.0 days compared to 7.4±13.4 days for the non-survivors, a short stay was significantly associated with neonatal mortality as the infants probably demised early (p <0.001). Fifty-eight per cent (33/57) of the non-survivors were early neonatal deaths vs 42%(24/57) late neonatal deaths.

Table 5: Univariate Logistic regression of infant outcome and birth weight

	Odd (95%CI)	p-value
Birth weight (g)		
1100-1499	Ref	
1000-1099	3.6(1.4;8.8)	0.004
900-999	2.1(0.7;6.5)	0.164
800-899	10.9(3.6;32.9)	<0.001
600-799	11.8(3.6;38.4)	<0.001

4.4.2 Infant conditions as risk factors for neonatal deaths

Of the infants eligible for this study, according to the neonatal records 77% (195/252) versus 68% (156/231) of PPIP data survived. Of the deaths 15%(34/231) were 1000g-1499g and 18%(41/231) ELBW from the PPIP data, 13% (33/252) were 1000g-1499g and 10%(24/252) were ELBW from the neonatal records respectively.

Table 6: Infant conditions as risk factors for neonatal deaths

	Total babies n=252(%)	Survivors n=195(%)	Non-survivors n=57(%)	p-values
Sepsis	118(47)	80(41)	38(67)	0.001
Probable	90(76)	62(78)	28(74)	0.649
Proven	28(24)	18(22)	10(26)	
Early (≤7)	78(31)	51(26)	27(47)	0.434
Late (≥7-28)	40(16)	29(15)	11(19)	
RDS	86(34)	45(23)	41(71)	<0.001
Pulmonary hemorrhage	12(5)	0	12(21)	<0.001
Pneumonia	25(10)	22(11)	3(5)	0.181
Hypothermia	89(35)	60(31)	29(51)	0.005
Hypoglycaemia	37(15)	26(13)	11(19)	0.263
Neonatal jaundice	179(71)	150(77)	29(51)	<0.001
Necrotising enterocolitis	5(2)	2(1)	3(5)	0.044
IVH	4(2)	2(1)	2(4)	0.187
Patent Ductus Arteriosus	4(2)	4(2)	0	0.276
ROP				
Yes	0	0	0	-
No	252	0	0	
Bronchopulmonary dysplasia				
Yes	18	16	2	0.226
No	234	179	55	

Infant variables associated with higher mortality included RDS (p <0.001), Pulmonary hemorrhage (p <0.001), NEC (p =0 .044), followed by Sepsis (p = 0.001) and Hypothermia (p = 0.005). Majority 71%(41/57) of the non-survivors had hyaline membrane disease and up to 67%(38/57) of these infants had sepsis. A high number 35%(89/252) of the neonates and 51%(29/51) of the non-surviving infants had hypothermia on admission from the labour ward. None of the babies with pulmonary haemorrhage survived.

Pneumonia (p = 0.181), Early or late sepsis (p=0.434), Probable or proven sepsis (p=0.649), BPD(p=0.226) and Hypoglycaemia (p = 0.263) were not found to be associated with higher mortality; however, on admission, 15% of the babies had hypoglycaemia, which is avoidable. Seventy one percent 71%(/179/252) of the neonates had neonatal jaundice, which was statistically significantly associated with survival (p <0.001), however this was probably a coincidental finding as the literature does not associate jaundice with improved survival.

Two per cent (4/252) of the study population had a confirmed intraventricular haemorrhage and was not associated with mortality (p= 0.187), however this was likely under-reported and so the non-significance to outcome in this study may not be a true reflection, and 2%(4/252) of the patients had cardiac echocardiography confirmed patent ductus arteriosus and none of them died. ROP screen was done in 1%(2/252) of these infants during the hospital stay, probably because the screen was done as out patients, therefore under reported in this study.

4.4.3 Maternal characteristics associated with mortality

Overall 252 mothers paired with their infants were included in this study. The mean age of mother of the survivors was higher than the non-survivors (26.8±6.8 versus 25.2±6.1 and was not statistically significant (p=0.1132). A greater proportion 68% (39/68) of the non-survivors were born from mothers between the age 20-34 years compared to survivors 69% (135/195), overall this was not statistically significant (p=0.552).

Table 7: Maternal characteristics as a risk factors for neonatal mortality

	N=252 n (%)	Survivors n=195 (%)	Non-survivors n=57 (%)	p-values
Maternal age (years)		26.8±6.8	25.2±6.1	0.1132
<20	33(13)	23(70)	10(30)	0.552
20-34	174(69)	135(78)	39(12)	
35+	43(17)	35(81)	8(19)	
Not recorded	2(1)	2(100)	-	
Parity				
0	90(36)	65(72)	25(28)	0.310
1-3	124(49)	97(78)	27(12)	
>3	11(4)	9(82)	2(18)	
Not recorded	27(11)	24(89)	3(11)	
RPR				
Negative	241(95)	186(77)	55(23)	0.845
Positive	1(1)	1(100)	-	
Not recorded	10(4)	8(80)	2(20)	
HIV status				
Negative	200(79)	156(78)	44(22)	0.415
Positive	48(19)	37(77)	11(13)	
Not recorded	4(2)	2(50)	2(50)	
Treated				
Yes	41(85)	31(76)	10(24)	1.000
No	7(15)	6(86)	1(14)	
ANC Steroids				
No	16(6)	9(56)	7(44)	0.111
Yes	102(40)	81(79)	21(11)	
Not recorded	134 (54)	105(78)	29(22)	
Mode of delivery				
CS	139(55)	113(58)	26(46)	0.100
Normal	113(45)	82(42)	31(54)	

The mean parity was 1.0±1.21 and 36%% (90/252) were primigravida versus 54% multi parous, 11%(27/252) parity was not recorded. only 1% of the mothers were RPR positive and were treated, a small number 4% (10/252) were not recorded. The majority 79% (200/252) of the mothers tested HIV negative, 19%(48/252) tested positive and 85%(41/48) were on ARV's, a small number 2%(4/252) were not recorded. Fifty-five per cent (139/252) of these mothers delivered via caesarean section (CS), indications for CS were not recorded in most cases.

Antenatal steroids administration was associated with lower mortality (p =0.111), however this was under-reported as it was not documented in 53%(134/252) of the records, so the non-significance to outcome in this study may not be a true reflection.

4.4.4 Maternal conditions associated with mortality

The most commonly encountered maternal morbidities diagnosed by the admitting doctor in labour ward were, Pregnancy hypertensive disorders 46%(117/252) and Spontaneous (unexplained) preterm labour 31%(77/252). Maternal morbidities, such as Obstetric hemorrhage, Pregnancy hypertensive disorders, Abruption placenta, Premature rupture of the membrane and Placenta praevia were not significantly associated with neonatal deaths (p >0.05). There was a significant relationship between spontaneous preterm labour and neonatal mortality (p=0.031).

Table 8: Maternal conditions as risk factors for neonatal deaths

	n=252 n (%)	Survivors n=195 (%)	Non-survivors n=57 (%)	p-values
Obstetric hemorrhage	8(3)	7(4)	1(2)	0.487
Pregnancy hypertensive disorders	117(46)	94(48)	23(40)	0.296
Abruption placenta	4(2	4(2)	-	0.276
Preterm rupture of membranes	20(8)	16(8)	4(7)	0.770
Placenta praevia	6(2)	5(3)	1(2)	0.724
Spontaneous preterm labour	77(31)	53(27)	24(42)	0.031
Other	20(8)	16(8)	4(7)	0.770

4.4.5 Interventions as risk factors for neonatal deaths

Table 9 shows the different interventions as a predictor of neonatal mortality. Five per cent (13/252) required NCPAP, 22%(55/252) required SiPAP, 20%(51/252) required mechanical ventilation, 1%(1/252) required Surfactant only. Fifty-two per cent (132/252) of the infants did not require either Surfactant**,** or SiPAP, or NCPAP or Ventilation, these infants were probably bigger or SGA and more stable and did not require additional intervention. Twenty-one per cent (52/252) of the infants required Surfactant plus either SiPAP or NCPAP or Ventilation as interventions.

The use of NCPAP 0nly was not associated with increased mortality (p=0.471), 69%(9/13) of the infants survived. Among the infants who required SiPAP 69% (38/55) significantly survived (p=0.096). There was a significant relationship between the use of invasive ventilation and neonatal mortality (p <0.001), probably because the severely sick neonates who also did not cope on either NCPAP/SiPAP, and with weight of >1000g are eligible for invasive mechanical ventilation in this unit.

Table 10 shows the intervention as a predictor of neonatal mortality for Surfactant with either NCPAP or SiPAP or Mechanical Ventilation. Infants who required invasive ventilation and surfactant had a higher mortality of 56%(19/34) and significantly associated with poor outcome (p<0.001), these were probably very sick babies. Use of NCPAP and surfactant was not associated with increased mortality, none of these infants died (p=0.443). Sixty-three per cent (10/16) of the infants who required SiPAP with surfactant survived with a p=0.142.

Table 9: Intervention as a predictor of neonatal mortality

	n=252(%)	Survivors n=195(%)	Non-survivors n=57(%)	p-values
NCPAP	13(5)	9(69)	4(31)	0.471
SiPAP	55(22)	38(69)	17(31)	0.096
Ventilation	51(20)	23(45)	28(55)	<0.001
Surfactant only	1(1)	1(100)	-	0.588
None	132(52)	124(94)	8(6)	<0.001

Table 10: Intervention as a predictor of neonatal mortality for Surfactant with either NCPAP or SiPAP or Mechanical Ventilation

	n=52(%)	Survivors n=195(%)	Non-survivors n=57(%)	p-values
NCPAP + Surfactant	2(4)	2(100)	-	0.443
SiPAP + Surfactant	16(31)	10(63)	6(37)	0.142
Ventilation + Surfactant	34(65)	15(44)	19(56)	<0.001

4.5 Causes of infant death

The various causes of death, according to the PPIP classification and patient records, are shown in Table 10**.** The common cause of death for both ELBW and infants with BW 1000g -1499g, from both the PPIP at 43%(54/125) and medical records data at 51% (29/57) was multi-organ immaturity, followed by sepsis at 19%(24/125) and 21%(12/24) respectively.

Table 11: Causes of deaths for VLBW infant from PPIP and Medical Records

	PPIP (n=125)		Records (n=57)	
	No	%	No	%
Immaturity	54	43	29	51
Infection	24	19	12	21
HMD	9	7	6	11
Pulmonary Hemorrhage	9	7	5	9
Asphyxia	8	6	0	0
IVH	3	2	2	4
NEC	3	2	3	5
Miscellaneous	15	12	0	0

4.6 Conclusion

In this chapter, the results of the study were presented and interpreted. The chapter to follow discusses the findings of this study and compares these findings with the findings in previous studies.

CHAPTER 5

DISCUSSION AND CONCLUSION

5.1 Introduction

In this chapter, the results of the study are discussed and compared with the findings from other studies. This was the first study in the Mankweng Hospital with its main purpose to analyse the neonatal survival rate of VLBW and ELBW infants in the Neonatal Care Unit.

The chapter is subdivided in alignment with the objectives of the study as follows:

- To determine the prevalence and survival rate of very low and extremely low birth-weight infants;
- To describe risk factors associated with very low and extremely low birth-weight infant's mortality;
- To describe the causes of death amongst very low and extremely low birth weight infants.

5.2 Prevalence of very and extremely low birth-weight infants

In 2012 an estimate of 14% of all births globally were preterm and the number is rising, with up to 60% of the cases born in Sub-Saharan Africa and Asia (WHO, 2015; Lloyd et al., 2012). Therefore, prematurity is a global public health priority (Howson et al., 2013). In this study, the rate of preterm birth was estimated at 23% (PPIP data), which is higher than the overall global estimation.

In general, most studies in the literature looking at a similar population considered VLBW as birth weight as 500g-1500g, and ELBW as less than 1000g. In this study the prevalence rate of VLBW was 6.3% of the total live births. Of these, 4.7 % weighed 1000g–1499g and 1.6% were ELBW respectively. This finding is higher than in developed countries such, as USA and Europe, with a documented prevalence rate of VLBW at 3.4% and 1% of all live births, respectively (Numerato et al., 2015). Cardoso and colleagues, in their study conducted in Brazil, reported that 1.2% of the total live births were VLBW, which is lower than the rate reported in this study (Cardoso et al., 2013). In Africa, reports from Gabon, Togo and Cameroon indicate that the rate of prematurity can vary from 11.1% to 57% (Chiabi et al.,2013). In South Africa, Kirsten et al found that rate of prematurity is 22% and VLBW contributes 4 -5% of the total births, this is also lower than it was found in the current study (Kirsten et al., 2012).

In this study, based on the hospital records, VLBW represented 25% of the total admissions. According to the PPIP, 4.9% were ELBW and these neonates contributed up to 33%(41/125) of the total neonatal deaths and 55%(41/75) of babies with BW 500-1499g. A study at CHBH found that VLBW represented 3% of the total live births and 21% of the admissions, accounting for 55% of the total neonatal mortality (Velaphi et al., 2005). In a study at Steve Biko Academic Hospital (SBAH) Lloyd et al., found that 8.3% of neonatal admissions were classified as ELBW and 23.6% as VLBW (Lloyd et al., 2013). In another study at Madedeni Hospital, VLBW represented 3.7% of the total admissions, of these infants 24% were ELBW and 76% 1000g-1499g (Bondi et al.,2007)

The prevalence of prematurity and of VLBW in this study is comparable to other studies done in South Africa, although variable per country in Africa the rate can be higher than found in this study. Reasons for the higher prevalence of ELBW and VLBW in this study compared to developed countries was unclear. However, social and economic inequalities were noted to be associated with increased risk of preterm birth, even in developed countries, with early (<32 weeks) preterm birth rate twice as high in those who were poor and had lower education levels (Heather et al., 2016). In addition, studies have found that poverty contributes to a higher prematurity rate, with mothers from poor families being at high risk of premature birth (Cardoso et al., 2013; WHO, 2015).

Analysis of maternal socioeconomic status was not part of this study, but one can assume that low economic status may have contributed to the high prevalence of prematurity, as the population of Limpopo is approximately 80% rural, living in poor socioeconomic conditions (Limpopo Department of Health, 2016).

5.3 Survival rate of very and extremely low birth-weight infants

Based on the PPIP data 68%(156/231) vs 77%(195/252) from the medical records of this study population survived, the survival of extremely low birth weight infants was 29%(17/58) vs 52%(26/50) and 80%(139/173) vs 84%(169/202) for babies with a birth weight of 1000g-1499g respectively. Amongst the non-survivors, a significant higher proportion (71%) of the extremely low birth weight infants died as compared to those who survived (p=0.001), With regard to infant with birth weight 1000-1499g

(80%), 1500-1999g (91%), 2000-2499g (97%) and ≥2500g (99%) a significant greater proportion survived (p=0.001).

The results in this current study are comparable to other studies conducted in South Africa, i.e. 72% at CHBAH and 73% at CMJAH of babies with BW 500g -1499g survived (Velaphi et al., 2005; Ballot et al., 2015). However, this figure is lower than figures from developed countries like the USA, where 85% of infants survive to discharge (Horbar et al., 2012). In India, a developing country, the overall survival rate of the infants was 63% (Basu et al., 2008), which is lower to this study's findings.

From the neonatal records this study found that 84%(169/202) of those infants weighing 1000g-1499g survived, which is comparable to the 84% survival rate at CHBAH and 85.8% at CMJAH (Velaphi et al., 2005; Ballot et al., 2010). However, Ballot et al looked at survival of BW 1001g>1500g and these hospitals are quaternary hospitals, with better human and physical resources.

The findings of this study, from the PPIP and medical records data showed that 29%(17/58) to 52%(26/50) of those neonates who were ELBW survived, the difference in the survival rate may be because out-born babies were not captured in the PPIP data and that infants who died early in labour ward or theatre were excluded from the medical records data. The survival rate in this study is higher than 26.5% reported at CMJAH (Kalimba et al., 2013). However, this would be expected since Kalimba excluded all babies with birth weight of 901g-1000g. Several other studies done in South Africa, the USA and India reported the survival rate of ELBW

at 62.9%, 51.8% and 56.1%, respectively (Kirsten et al., 2012; Horbar et al., 2012; Amit et al., 2013). However, in these studies the infants had back-up ventilation.

Survival of infants is documented to vary from country to country, as well as hospital to hospital, depending on the quality of antenatal, intrapartum and neonatal care, as shown in this study. Therefore, it is very important that health professionals at obstetrics and neonatal units know the outcomes of these infants in their hospitals, their limitations and areas where they can improve (Velaphi et al., 2005; Rajin et al., 2011). In this study, in 54% of the mothers, it was unknown whether they were given antenatal steroids or not, of these 20% gave birth to ELBW this could have attributed to the higher mortality of these infants.

5.4 Risk factors associated with neonatal mortality

5.4.1 Maternal characteristics

Maternal factors such as young or advanced maternal age have been associated with an increased risk for preterm birth (Blencowe et al., 2013). However, in this study maternal age was not associated with the survival or mortality of the baby.

Studies have shown that the use of antenatal steroids improve survival rates and limits complications in premature infants, such as hyaline membrane disease, intraventricular haemorrhage, necrotising enterocolitis, respiratory support, intensive care admissions and systematic infections in the first 48 hour of life (Roberts et al., 2006; Carneiro et al., 2012; Kirsten et al., 2012). Antenatal steroids were not associated with survival ($p = 0.111$), however this was under-reported as it was not

documented in 53%(134/252) of the records, regardless of birth place, so the non-significance to outcome in this study may not be a true reflection. Therefore, it is of paramount importance to improve the patient record-keeping. Guidelines on use of antenatal steroids are available at all delivery sites and have to be strictly implemented.

5.4.2 Maternal morbidity

In this study, nearly half of the mothers were diagnosed with a pregnancy hypertension disorder (46%), followed by spontaneous preterm labour (31%) and preterm rupture of membranes (8%) This finding is similar to findings in a study conducted at the Tygerberg Hospital (Odendal et al, 2003). Spontaneous premature labour and delivery was associated with higher neonatal mortality (p=0.031), a finding that needs further investigation.

5.4.3 Infant characteristics

Many studies mentioned that prematurity occurs more often in male infants and that male infants are more likely to die compared to the female infants (Blencowe et al., 2013; YI-YU Su et al., 2016). In this study most of the infants were female, however, while there were more male than female infant deaths, this difference was not statistically significant. There was no significant association between the place of delivery and neonatal mortality (p >0.05), probably because only referrals within 24 hours of birth were included.

Gestation age in this study was mainly calculated by using the Ballard score, which was subjective as it was done by different medical officers or registrar with different

level of skills. Survival in this study significantly increased with both increasing gestation age and birth weight, confounded by the fact that only >1000g were offered invasive ventilation. Similar findings were reported in studies done in both developed and developing countries (Ballot et al., 2010).

Survival to hospital discharge improved with increase in BW ($p<0.001$) according to the neonatal records data, with a significant increase rate of survival from 33%(3/9) to 56%(23/41) of babies with BW<750g and 750g- 999g amongst the ELBW respectively. Infant weighing 600-799 (OR: 10.9, 95%CI:3.6;32.9; $p<0.001$) and 800-899 (OR: 11.8 95%CI: 3.6;38.4; $p<0.001$) were more likely to die compared to those with BW 1100-1499.This is universally found in other studies (Ballot et al., 2010; Carneiro etal., 2012; Velaphi et al.,2016)

In the present study, Apgar scores at 1 and 5 minutes were significantly higher in the survival group compared to the non-survivors. Several studies found the same results (Carneiro et al., 2012; Ballot et al., 2010). Although Apgar score is relatively subjective, it reflects on the intrapartum and the immediate postpartum care (resuscitation).

Noted in this study was the fact that babies who were resuscitated at birth were more likely to die ($p<0.002$). This might reflect on the skills of the health care workers, severity of the illness or immaturity of the infants. Wyckoff et al., found that approximately 10% of newborns require some assistance to begin breathing at birth; while less than 1% require extensive resuscitation measures, such as cardiac compressions and medications (Wyckoff et al., 2015). Training of birth attendants in

neonatal resuscitation in Tanzania was associated with a 47% reduction in all-cause newborn mortality in the first 24 hours (Arlington et al., 2017).

Studies showed that a greater proportion of low birth weight infants die within the first day of life in low- and middle-income countries, compared to high-income countries (Mohamed et al., 2010). Similarly, in this study a greater number of the survivors stay significantly longer in the hospital, mostly for weight gain purposes but this is unsurprising since length of stay will be truncated by death.

5.4.4 Neonatal Morbidity

Ballot found that NEC and hypotension were significantly related to mortality (Ballot et al., 2010). In this study, according to the PPIP and medical records data, common causes of death were multi-organ immaturity followed by sepsis, with no difference between ELBW and infants with BW 1000g - 1499g which is a similar finding in a study done at CHBH (Velaphi et al., 2005). From the medical records other factors such as hypothermia ($p=0.005$), HMD ($p<0.001$), pulmonary haemorrhage ($p<0.001$) and NEC ($p=0.044$), contributed to mortality.

A high number 35%(89/252) of the neonates and 51%(29/51) of the non-surviving infants had hypothermia on admission from the labour ward, this was statistically significant ($p=0.005$). Studies have shown an increased mortality, morbidity, risk of late onset sepsis, IVH and worsening of respiratory distress associated with moderate to severe hypothermia (Datta et al., 2017). Multiple factors can lead to hypothermia on admission this can be different from each facility, it is imperative for

health care workers to identify the key factors contributing to hypothermia and develop strategies to address them. The simple expedient of covering infants <1200g or <28 weeks gestation with polyethylene or plastic immediately after delivery, in conjunction with hats and socks, warm delivery rooms and functioning incubators or radiant warmers reduces hypothermia (Lloyd et al., 2103)

Many studies have shown that the use of antenatal steroids can improve survival and reduce severity of complications, such as RDS, NEC and IVH (Kalimba et al., 2013; Kirsten et al., 2012; Lloyd et al., 2013). In this study antenatal steroids were not associated with better survival (p =0.111), however this was under-reported as it was not documented in 54%(134/251) of the records, regardless of birth place, so the non-significance to outcome in this study may not be a true reflection. Therefore, it is of paramount importance to improve the patient record-keeping. Guidelines on use of antenatal steroids are available at all delivery sites and have to be strictly implemented.

Although sepsis was associated with poor outcome (p <0.001), neither culture proven or probable sepsis of either early or late onset was associated with mortality. Only 24% of the infants had a culture proven sepsis this is comparable 29% found at CHBH (Velaphi et al., 2005), reasons for low sensitivity in both studies could be that less than 1ml of blood was collected, prenatal antibiotic use, level of bacteraemia and laboratory capabilities. Blood culture is the gold standard for the diagnosis of neonatal sepsis, multiple cultures could help increase the yield of this test (Zea-vera et al., 2015). It is imperative to have culture proven sepsis diagnosis, as this will guide antibiotics stewardship.

Physiological jaundice is a common complication of birth prematurity, with a peak of up to 80% of preterm infants diagnosed with this condition towards the end of the first week of life (Kalimba et al., 2013; Amit et al., 2013). Seventy one percent 71%(/179/252) of the neonates had neonatal jaundice, which was statistically significantly associated with survival ($p < 0.001$), however this was probably a coincidental finding as the literature does not associate jaundice with improved survival.

Cranial sonar was only documented in 2% of the infants in this study, this may have been probably because most of neonates were referred to their local hospitals for weight gain as soon as they were stable, some infants may have died before it could be done. This was likely under-reported and so the non-significance to outcome in this study may not be a true reflection. A study in India showed that up to 22.5% of ELBW/VLBW infants had intraventricular haemorrhage (Amit et al., 2013).

Studies have shown the prevalence rate of retinopathy of prematurity to be 17-22%, especially in ELBW infants (Van der Merwe et al., 2013; Dadoo et al., 2016). In this study, according to the neonatal records, only two infants were screened for ROP and of the two, none was found to have ROP. The main reason was that all babies eligible for ROP screening thus those with birth weight of <1500g or <32 weeks gestational age, were booked as outpatient because of shortage of staff at ophthalmology department. Only 2% of the patients had cardiac echocardiography confirmed patent ductus arteriosus and none of them died. At the time of the study

there was only one general paediatrician at the hospital who was competent with ECHO and only babies suspected of having other cardiac problems had ECHO.

5.4.5 Interventions

Overall, more than half (52%) of the infants in this study did not require surfactant, NCPAP, SiPAP or mechanical ventilation intervention. This represents a significantly high proportion of survivors compared to non-survivors, these infants were probably bigger and more stable and did not require additional intervention.

Most studies have shown improved survival of VLBW infants and decreased need for ventilation with the use of NCPAP/SiPAP with or without surfactant, with survival rate of 80–87% (Kirsten et al., 2013; Bopape-Chinyanga et al., 2016). One of the recommendations of NAPEMMCO is to use NCPAP/SiPAP in most district and regional hospitals. Low cost methods like bubble CPAP have also been shown to improve survival of premature infants and equipment does not have to be expensive (Bateman,et al 2013). In the current study, 27% of the infants used NCPAP or SiPAP only, this was associated with improved outcome in both interventions the survival rate was 69%. Use of NCPAP and surfactant was not associated with increased mortality, none of these infants died (p=0.443). Sixty-three per cent (10/16) of the infants who required SiPAP with surfactant survived with a p=0.142.

In a limited resource country like South Africa, some public hospitals still use a cut-off of 1000g for invasive ventilation, unlike in developed countries (Bondi et al., 2007). In this study on logistic regression of infant outcome and birth weight, there

was a marked improved survival from BW 900g-999g (OR 2.1;95%CI: 0.7 - 6.5; p=0.164) and significantly improved survival of infants from BW 1000g-1099g (OR 3.61;95%CI:4 - 8.8; p=0.04) compared to infants with BW 1100g-1499g. This could be probably because due to limited resources invasive mechanical ventilation is mainly afforded to infants with BW >1000g, especially those who are very sick or not coping on the non-invasive ventilation, like NCPAP or SiPAP, hence, the high rate of infant deaths of 55% (p<0.001) amongst those mechanically ventilated. Velaphi and co-workers recommended a change in policy to ventilate infants with weight <1000g, starting at least at 900g, as these infants with BW of 900g-999g had improved survival to 50%, compared to 37% in those infants <900g in their study. This would improve the overall infant survival rate and neonatal mortality rate to match the levels associated with developed countries (Velaphi et al., 2005).

5.5. Conclusion

Prematurity remains a major public health concern, especially in low- and middle-income countries. The lower prevalence and better survival rate observed amongst infants in developed and developing countries like Brazil suggests that achieving this goal is possible. Reliable continued data collection from neonatal networks, for example PPIP, can help identify problems and lead to policy making, to improve neonatal care at all levels.

Based on the findings, the following recommendations are made:

- Reliable data and further research should address effective steps to prevent preterm labour and extreme prematurity;

- Consider using weight cut-off >900g for ventilation
- Implement and document obstetrics use of antenatal steroids at all levels;
- Improve human resources, as well as the availability of equipment such as NCPAP, SiPAP and mechanical ventilators. “Low cost” methods like bubble CPAP have also been shown to improve survival of premature infants and equipment does not have to be expensive.
- Prevention of hypothermia: with use of polyethylene or plastic immediately after delivery, in conjunction with hats and socks, warm delivery rooms and functioning incubators or radiant warmers especially during resuscitation
- Strive to have more proven sepsis diagnosis as this will influence antibiotic stewardship;
- HBB workshops can help to improve neonatal resuscitation skills, as well as train health care workers on measures to prevent hypothermia; and
- Improve patient record keeping.

5.6. The Study limitations

- This was a retrospective study therefore more likely to have missing data
- The definition and weight cut-off for ELBW and VLBW differed in other studies found in literature
- Exclusion of those who died immediately in labour ward may have influenced the high rate of survival found in this study

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ANNEXURE C: DATA COLLECTION TOOL

A.	**MOTHERS INFORMATION**								
A1	Age (years)		**A2**	Parity		**A3**	Gravidity		
A4	RPR Status	Positive		**A5**	If positive, was it treated		Yes		

		Negative					No	
A6	HIV Status	Positive		**A7**	If positive, patient on ARV:		Yes	
		Negative					No	
A8	Received Antenatal steroids		Yes		**A9**	Mode of delivery	Normal	
			No				CS	
A9	Obstetric Diagnosis							
B.	**NEWBORN INFORMATION**							
B1	Gender	Male		**B2**	Gestational age			
		Female						
B3	Place of delivery	Referred		**B4**	Birth weight			
		Inborn						
B5	APGAR score				Resuscitation	Yes		
						No		
B6	Complications:							
		Sepsis:	Y	N	Early onset		Late onset	
					probable		probable	
					proven		proven	
		Respiratory Distress Syndrome	Y	N				
		Pulmonary Hemorrhage	Y	N				
		Pneumonia	Y	N				
		Bronchopulmonary dysplasia	Y	N				
		Hypothermia	Y	N				
		Hypoglycemia	Y	N				
		Neonatal jaundice	Y	N				
		Necrotising Enterocolitis	Y	N				
		Retinopathy of Prematurity	Y	N				
		Intraventricular Hemorrhage	Y	N				
		Patent Ductus Arteriosus	Y	N				
B8 Intervention		Surfactant			Nasal CPAP/SiPAP		Ventilation	
		Admin date:			Discharge date			
B9	Outcome	Discharged		**B10**	If died, causes of death			
		Died						

ANNEXURE D: Clearance Certificate from TREC

University of Limpopo
Faculty of Health Sciences
Executive Dean
Private Bag X1106, Sovenga, 0727, South Africa
Tel: (015) 268 2149, Fax: (015) 268 2685, Email:noncebamk@ul.ac.za

DATE: 07 JUNE 2016

NAME OF STUDENT:	MASHEGO M.P.A
STUDENT NUMBER:	19925147
DEPARTMENT:	PAEDIATRICS AND CHILD HEALTH
SCHOOL:	MEDICINE
QUALIFICATION –	MMED

Dear Student

FACULTY APPROVAL OF PROPOSAL (PROPOSAL NO. FHDC2016/4/5-13)

I have pleasure in informing you that your MMED proposal served at the Faculty Higher Degrees Meeting on 07 JUNE 2016 and your title was approved as follows:

Approved Title: Survival of Very Low Birth and Extreme Low Birth Weight Infants at Mankweng Neonatal Care Unit.

Note the following:

Ethical Clearance	Tick One
Requires no ethical clearance Proceed with the study	
Requires ethical clearance (TREC) (apply online) Proceed with the study only after receipt of ethical clearance certificate	√

Yours faithfully

Prof NP Mbambo-Kekana
Executive Dean: Faculty of Health Sciences

Prof L. Skaal
Chairperson

CC: Supervisor: Prof N Shipalana

Finding solutions for Africa

ANNEXURE E: Letter of approval from the Department of Health, Limpopo

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Enquiries: Latif Shamila (015 293 6650)

Ref:4/2/2

Mashego MPA
University of Limpopo
Private Bag X1106
Sovenga
0727

Greetings,

RE: Survival of very low birth and extreme low birth weight infants at Mankweng Neonatal Care Unit

The above matter refers.

1. Permission to conduct the above mentioned study is hereby granted.
2. Kindly be informed that:-
   - Research must be loaded on the NHRD site (http://nhrd.hst.org.za) by the researcher.
   - Further arrangement should be made with the targeted institutions, after consultation with the District Executive Manager.
   - In the course of your study there should be no action that disrupts the services.
   - After completion of the study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
   - The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
   - The above approval is valid for a 3 year period.
   - If the proposal has been amended, a new approval should be sought from the Department of Health.
   - Kindly note, that the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated.

Head of Department

06/10/2016
Date

18 College Street, Polokwane, 0700, Private Bag x9302, POLOLKWANE, 0700
Tel: (015) 293 6000, Fax: (015) 293 6211/20 Website: http/www.limpopo.gov.za