VENTILATORY SUPPORT AND SURFACTANT USE IN EXTREMELY LOW BIRTH WEIGHT INFANTS OVER A DECADE AT A TERTIARY HOSPITAL IN JOHANNESBURG, SOUTH AFRICA

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Declaration

I**,** Minah Nthodi Mavunda, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or other university.

Signature of candidate:  Date: 27/04/2023

Acknowledgements

I would like to thank Prof Ballot and Dr Ramdin for their guidance and unwavering support. Many thanks to Rossella Bandini and Charlotte Maxeke Johannesburg Academic Hospital staff involved in data collection for the neonatal unit.

Dedication

I am dedicating this research report to my parents and siblings (Emily, Annah, Amon, Bob, Sam, Jnr and Kate). Thank you for the love and support throughout my specialising journey.

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Abbreviations

BBA: Born before arrival

CLD: Chronic lung disease

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

CMV: Conventional mechanical ventilation

ELBWI: Extremely low birth weight infants

FiO2: Fraction of inspired oxygen

HIV: Human Immunodeficiency Virus

ICU: Intensive care unit

InSurE: Intubation, surfactant and extubation

IVH: Intraventricular haemorrhage

NCPAP: Nasal continuous positive airway pressure

NEC: Necrotising enterocolitis

NMR: Neonatal mortality rate

PaCO2: Partial pressure of carbon dioxide

PaO2: Partial pressure of oxygen

RDS: Respiratory distress syndrome

ROP: Retinopathy of prematurity

SRT: Surfactant replacement therapy

TCH: Tygerberg Children's Hospital

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Ventilatory support and surfactant use in extremely low birth infants over a decade at a tertiary hospital in Johannesburg, South Africa

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Abstract

Background: In Southern Africa, extremely low birth weight infants (ELBWI) are a major contributor to neonatal mortality and morbidity. The ELBWI are at the greatest risk of respiratory distress syndrome (RDS), and the severity of RDS is inversely related to gestational age.

Objective: To review ventilatory support and surfactant use in ELBWI and its effect on survival of ELBWI at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), South Africa.

Methods: This was a secondary analysis of an existing database of ELBWI admitted at CMJAH neonatal unit from 01 January 2008 to 31 December 2017. The different modes of respiratory support were compared for survivors and non survivors.

Results: A total of 1 184 ELBWI were enrolled in the study with a mean birth weight of 823.6g. Respiratory distress syndrome was diagnosed in 93.2% (1 103/1 184) infants, with 88.2% (1 044/1 184) receiving respiratory support. Respiratory support was offered in the form of surfactant replacement therapy (SRT), nasal continuous positive airway pressure (NCPAP) and/or conventional mechanical ventilation (CMV). Eighty one percent (706/902) of the infants received SRT, 62% (706/1 146) received NCPAP and 20% (225/1 135) received CMV. The survival of ELBWI who received SRT was 88.3% ($p<0.001$) and for infants who received NCPAP was 65.2% ($p=0.019$). Conventional mechanical ventilation was not associated with increased survival, 19.2% ($p=0.677$). The overall survival of ELBWI during the study period was 46% (540/1184).

Conclusion: The implementation of SRT and NCPAP are effective in the management of RDS in ELBWI.

KEYWORDS: extremely low birth weight infant, surfactant, ventilation, continuous positive airway pressure

INTRODUCTION

Extremely low birth weight infants (ELBWI) are a major contributor to neonatal mortality and morbidity. This increased mortality and morbidity is mainly attributed to respiratory distress syndrome (RDS), which is primarily the disorder of pulmonary surfactant deficiency in immature lungs.[1] The immature lungs have decreased compliance which is likely to cause atelectasis.[2,3] This in turn will lead to ventilation-perfusion mismatch, severe hypoxaemia and hypercarbia.[2,3] Furthermore, there is added risk of lung injury from invasive respiratory support.[2,3]

Treatment of RDS begins antenatally with administration of maternal steroids to pregnant women who are at risk of preterm labour between 24 to 34 weeks gestation. Once the infant is born and has features of RDS clinically and/or radiologically, exogenous surfactant can be administered via the less invasive surfactant administration or minimally invasive surfactant technique.[1]

Exogenous surfactant therapy increases the surfactant storage pool in preterm infants (which is approximately 4-5mg/kg at birth compared to 100mg/kg in term infants) and improves pulmonary gas exchange until enough endogenous surfactant is released from the storage pool.[1]

Since it was first described in 1971, nasal continuous positive airway pressure (NCPAP) has been widely used as a non-invasive mode for respiratory support in the management of RDS.[1-4] NCPAP provides continuous positive pressure which helps to recruit collapsed or fluid filled alveoli, thus improving perfusion ventilation mismatch, and increasing the functional residual capacity thereby improving oxygenation in the neonate.[1,3,4] The early use of NCPAP in premature infants reduces the need for surfactant replacement therapy (SRT) and invasive respiratory support.[4]

Neonatal intensive care is extremely expensive and in resource limited settings, such as South Africa, ventilatory support is only provided to neonates above 750-900grams (depending on institution). Smaller and more premature infants have increased morbidity, mortality and prolonged hospital stay.

Surfactant replacement therapy, NCPAP and conventional mechanical ventilation (CMV) remain the mainstay of therapy for RDS. This study aims to review surfactant use and ventilatory support of extremely low birth weight infants (ELBWI) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) neonatal unit over ten years. We can use this data to inform policies on intensive care unit (ICU) admission and management of ELBWI.

Methods

This was a secondary analysis of an existing database of ELBWI admitted at CMJAH neonatal unit. CMJAH is a tertiary hospital in Johannesburg, South Africa. The sample population included all ELBWI admitted to the neonatal unit within 48 hours of life from the 1st January 2008 to the 31st December 2017. Infants who died in the delivery room were excluded. Extremely low birth weight infants who were born at outlying primary level hospitals and clinics and those who were born before arrival (BBA) to hospital were admitted to the neonatal unit, therefore, they formed part of the study population.

The following definitions were used in the study:

- **Extremely low birth weight infants (ELBWI)**: infants with a birth weight less than 1000g.
- **Outborn**: infants who were not born at CMJAH.
- **Respiratory distress syndrome (RDS)**: diagnosed clinically with the following features tachypnoea, nasal flaring, subcostal and/or intercostal recessions, tracheal tug, grunting and oxygen saturation below 90%.
- **Chronic lung disease (CLD)**: persistent oxygen requirements up to or beyond 28 days of chronological age.
- **Necrotising enterocolitis (NEC)**: NEC II or III according to Modified Bell's staging criteria.[5]
- **Retinopathy of prematurity (ROP)**: ROP stage 3 or 4 according to the International Committee for the Classification of ROP.[6]
- **Intraventricular haemorrhage (IVH)**: bleeding in the lateral ventricle or parenchyma of the brain as observed on cranial ultrasonography. Papile scoring system was used for grading IVH for grade 3 to 4.[7]
- **NCPAP failure**: as either the infant has signs of worsening respiratory distress on NCPAP, increased oxygen requirements or respiratory failure ($pH<7.25$ with $Pa0_2<$ 60mmHg and/or $PaC0_2>55$mmHg
- **Resuscitation at birth**: ventilation with bag-mask valve or T-piece resuscitator and/or chest compressions.

Infants with birth weight above 750g were offered NCPAP and SRT from 2006/2007. The weight cut-off for mechanical ventilation was decreased from 900g to 800g in 2014. Some ELBWI below 800g without co-morbidities were occasionally offered mechanical ventilation. When all NCPAP machines were in use, some infants received SRT while on nasal prongs oxygen while awaiting NCPAP.
According to the CMJAH neonatal protocol the requirements for surfactant replacement therapy are as follows:

- Infant less than 37 weeks gestation
- RDS change on chest X-ray
- Preterm infant with increasing respiratory distress and oxygen requirements
- Preterm infant who is on NCPAP or CMV requiring Fi02 of $\geq 40\%$ to maintain oxygen saturation above 89%
- Infant must be haemodynamically stable

The following are the indication for ventilatory support:

- Respiratory failure
- Severe work of breathing: increasing respiratory rate, nasal flaring, grunting
- Severe or recurrent apnoeas
- Post operative

The unit is affiliated with a high care obstetric unit but has no infertility program. The neonatal team consists of neonatologists, neonatology fellowship candidates, registrars, medical officers, and interns.

Study setting

The neonatal unit at CMJAH had 104 beds. It had 14 beds in neonatal/paediatric intensive care unit (shared with paediatric surgery), 40 beds in high care, 40 beds in low care and 10 beds in nursery. Approximately 9 000 deliveries occurred at CMJAH over a year.

Ethics

The research protocol was approved by the Human Research Ethics Committee of the University of Witwatersrand. Ethics clearance certificate number M200548.

Database

The neonatal records were retrieved from Microsoft Access (2006-2012) and Research Electronic Database Capture (REDCap™) [8] hosted by the University of the Witwatersrand subsequently. The data was captured by attending neonatal staff upon discharge or death of the infant using hospital records for the purpose of clinical audit and quality improvement. Permission was granted by the host of the databases to access the data.

Data analysis

All data was de-identified – i.e., name, surname, hospital number, place of birth, date of admission was all removed prior to analysis. The collected data was captured in a Microsoft Excel spreadsheet for data cleaning and coding purposes and imported to the Statistic programme, Statistical Package for the Social Sciences (SPSS) version 25 IBM for analysis.

Descriptive statistics were presented in frequencies and percentages for categorical variables. Continuous variables were described using mean and standard deviation for the variables with normal distribution. Median and interquartile ranges (IQR) were used for variables that were not normally distributed.

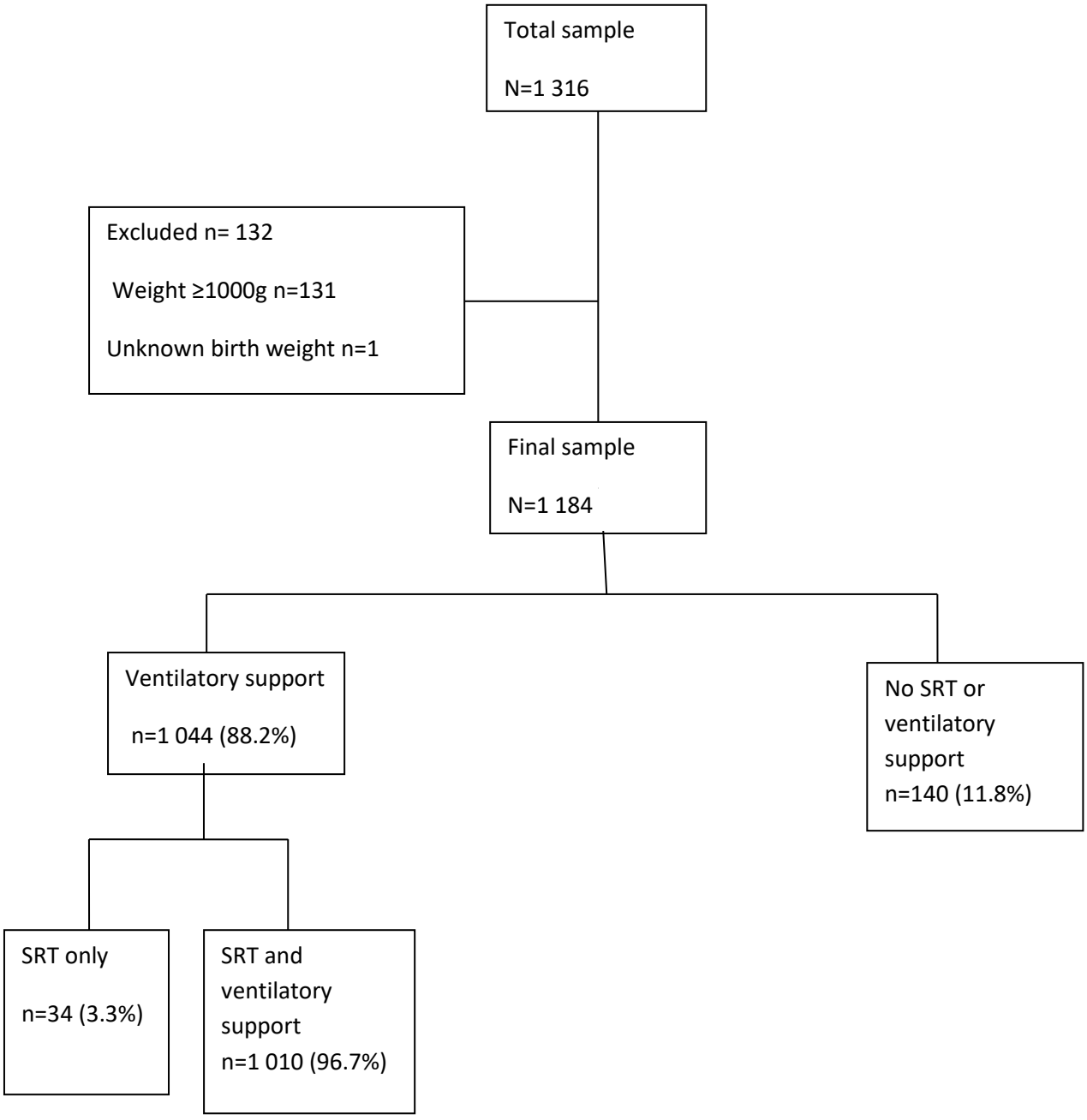
Comparisons between ELBWI who died versus those who survived were analysed using the Pearson chi-square and Fisher's exact tests for categorical variables. The unpaired t- test was used to compare continuous variables with a normal distribution. Mann -Whitney test was used for continuous variables that were not normally distributed. Patients that were transferred out to other hospitals were grouped with those that were discharged home and classified as survivors for statistical analysis.

Only valid cases were analysed for each variable (i.e., those with missing data were excluded). A p-value of <0.05 was considered significant.

Results

There was a total of 1 316 ELBWI on the database during the study period and 132 infants were excluded. The final sample size was 1 184 ELBWI as illustrated in Figure 1. The mean birth weight was 823.6g (SD 119.4) with a mean gestational age of 27 weeks (SD 2.1). The mean length of hospital stay was 30 days (SD 30.8) with the longest hospital stay of 204 days. The neonatal and maternal characteristics are summarised in Table 1 below. Females accounted for 53.3% (631/1 184) of the study population. Seventy two percent (848/1 184) infants had a screening cranial sonar, with 191/848 (16%) having IVH. Of the infants screened for retinopathy of prematurity (ROP), 63/899 (5.3%) developed ROP.

Figure 1: Study participants in the study reviewing ventilatory support and surfactant use in extremely low birth weight infants at Charlotte Maxeke Johannesburg Academic Hospital between 2008 and 2017



*SRT=Surfactant replacement therapy

Table 1: The maternal and extremely low birth weight infants' characteristics at Charlotte Maxeke Johannesburg Academic Hospital between 01 January 2008 and 31 December 2017

Variables	Total sample n/N (percentage%)
Maternal characteristics	
Antenatal care (at least one visit)	757/1 184 (64)
Antenatal steroids	481/1 184 (41)
Maternal hypertension	320/1 184(27)
Maternal diabetes	7/1 184 (1)
Maternal HIV	316/1 184 (27)
Maternal syphilis	14/1 184(1)
Multiple pregnancy	204/1 144 (18)
Chorioamnionitis	24/1 184 (2)
Attempted termination of pregnancy	35/1 184 (3)
Mode of delivery	
Vaginal delivery	565/1 134 (50)
Caesarean section (elective and emergency)	569/1 134 (50)
Neonatal characteristics	
Inborn	1 023/1 175 (87)
Resuscitation in the delivery room	698/1 184 (59)
Died within 12hours of admission	55/643 (9)
Surfactant replacement therapy	733/902 (81)
NCPAP	706/1 146 (62)
Conventional mechanical ventilation	225/1 135 (20)
Complications of prematurity	
Neonatal sepsis	527/1 184 (45)
Patent ductus arteriosus	117/1 173 (10)
Necrotising enterocolitis	71/1 175 (6)
Pneumothorax	10/1 171 (1)
Chronic lung disease	271/1 164(23)

HIV= Human Immunodeficiency Virus; NCPAP= Nasal continuous positive airway pressure

The overall survival of ELBWI was 46% (540/ 1 184). Respiratory distress syndrome was diagnosed in 1 103/1 184 (93.2%) of ELBWI.

Table 2 shows the effect of SRT, NCPAP and CMV on the outcome (survival or death) of the ELBWI during the study period. Place of birth was not significantly associated with survival, with inborn infants (1 023/1 175, 87%) and outborn infants (152/1 175, 13%) with survival rate of 46% and 41% respectively, p=0.258. Figure 2 shows how the rate of survival increased with increasing birth weight. Fifty three percent of ELBWI with a birth weight of 800g survived.

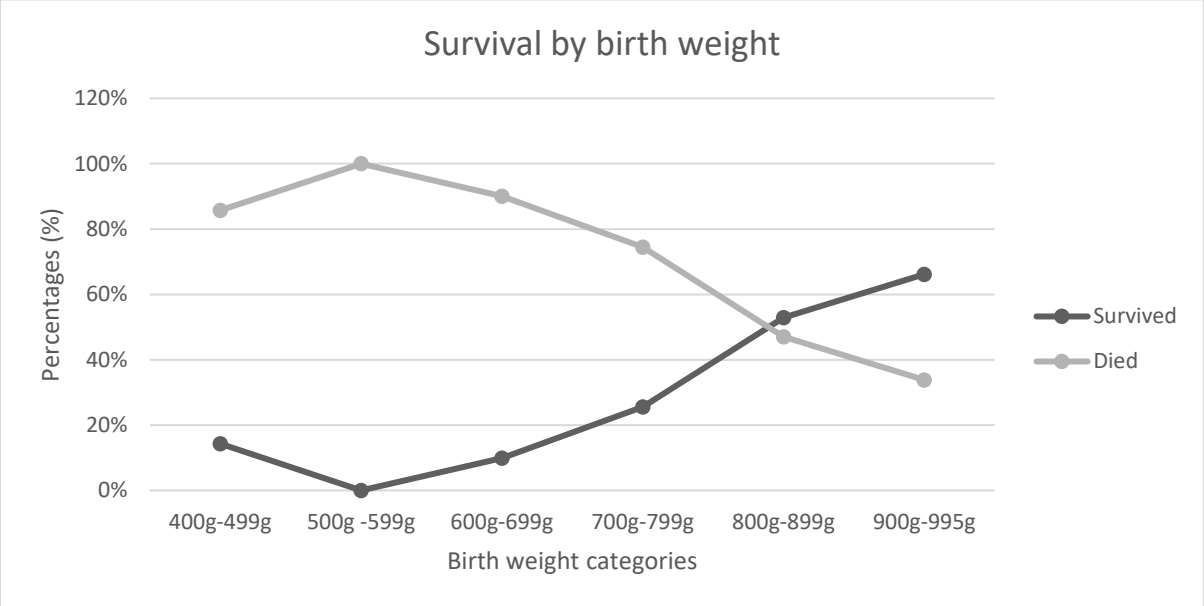
Table 2: The effects of surfactant replacement therapy and ventilatory support on survival of ELBWI at Charlotte Maxeke Johannesburg Academic Hospital between 01 January 2008 and 31 December 2017

Intervention	Died n/N* (%)	Survived n/N* (%)	p value
Surfactant	377/499 (75.5%)	356/403 (88.3%)	<0.001
NCPAP	359/614 (58.5%)	347/532 (65.2%)	0.019
CMV	124/611 (20.2%)	101/524 (19.2%)	0.677
CMV>749g	120/378 (31.7 %)	97/490 (19.7%)	0.001

*Denominators are different because of missing data

SRT= Surfactant replacement therapy; NCPAP= Nasal continuous positive airway pressure
CMV=Conventional mechanical ventilation

Figure 2: Percentage survival by birth weight for extremely low birth weight infants admitted at Charlotte Maxeke Johannesburg Academic Hospital from 01 January 2008 to 31 December 2017



Discussion

The study reviewed the effect of respiratory support in ELBWI over 10 years. Respiratory distress syndrome was diagnosed in 93.2% of ELBWI with 88.2% receiving respiratory support. Respiratory support was offered in the form of either SRT, NCPAP and/or conventional mechanical ventilation. The study demonstrated improved survival with the use of surfactant and NCPAP. Surfactant replacement therapy and NCPAP were associated improved survival, 88.3% and 65.2% respectively. The study conducted at Tygerberg Children's Hospital (TCH) in Cape Town showed survival of 63.4% and 80% for infants who

were treated with InSurE (intubation, surfactant and extubation) and NCPAP only respectively.[9] The introduction of bubble CPAP in Uganda, resulted in decrease in mortality rate of ELBWI from 75% to 61.1%.[10] The study by Kalimba et al,[11] conducted at CMJAH between 2006 to 2010, showed survival of 27.1% of ELWBI treated with NCPAP which has greatly improved over the years. This improvement was evident in the study conducted at CMJAH, comparing the survival of infants weighing 750-900g between 2006/2007 and 2013, which showed that survival for these infants more than doubled from 20.4% to 52.4%.[12] The improvement was attributed to the provision of NCPAP and surfactant, as the use of NCPAP increased by more than 13 folds in 2006/2007 (6.8%) and 2013 (94.8%).[12]

Two hundred and seventeen infants >749g received CMV, with 97 infants surviving to discharge. Conventional mechanical ventilation was not associated with increased survival, similar to the study conducted at Steve Biko Academic Hospital.[13] This might be explained by the fact that, CMV is offered to the sickest infants. Infants are initially managed with SRT and NCPAP. If the infant doesn't show clinical improvement and/or deteriorates while on NCPAP, then the infant is offered CMV if neonatal ICU bed is available. Due to different weight cut off for respiratory support in various institutions in Gauteng, the infants cannot be transferred to other institutions for CMV.

The overall survival in our study was 46% which shows improvement compared to the previous studies conducted in the same unit between 2006-2010[11] and 2013-2015[14], with survival rates of 26.5% and 40% respectively. A study done at TCH, showed a higher survival rate of 75%, but their study population was from 500g to 1000g and infants who died shortly after birth and outborn infants were excluded. [9]

The improved survival rate in our study, was likely due to changes in ventilatory support implemented over the years. In the present study, the birthweight for 50% survival was around 800g, compared to 900g in the previous research conducted by Ballot et al at CMJAH. [14] These results most likely reflect the impact the changes in respiratory support made in improving survival of ELBWI in our setting. The weight cut off for mechanical ventilation was reduced from 900g to 800g at CMJAH in 2014. In 2015, the unit tried to move away from birth weight altogether and offered all ELBWI surfactant replacement therapy and NCPAP, provided the infant has a satisfactory medical condition and availability of resources. A prospective observational study conducted in Cape Town demonstrated that with removal of SRT, NCPAP and CMV, the mortality rate for ELBWI will increase by 51%.[15] The use of NCPAP in ELBWI has greatly improved from 37.5% in 2010[11], to 81% during the study period.

At times, due to limited resources, not all infants who qualified for NCPAP could receive it. It is important to note that during the study period, there was a delay in initiating NCPAP as there was no labour ward facility for providing NCPAP. Early initiation of NCPAP is noted to be associated with reduced need for SRT and CMV. [4]

The higher birth weight was associated with improved survival with 66% of ELBWI weighing 900-995g surviving as illustrated in Figure 2. Twenty three percent of the ELBWI

who received ventilatory support developed chronic lung disease, which may reflect the improving survival of these infants. It is reassuring that only 1% of the infants developed pneumothorax as it is one of the complications of ventilatory support. The antenatal steroids usage in our setting is still low at 41% compared to other low-middle income countries [16] with an average of 52% and high-income countries with an average of 80% antenatal steroids coverage. [17] This can be attributed to the fact that most of the mothers presented to hospital already in advanced labour, and unbooked mothers are unlikely to have received antenatal steroids.

Extremely low birth weight infants account for 60% of premature deaths in South Africa, which makes it a significant contributor to Neonatal Mortality Rate (NMR). [18] From the results, NMR can be improved by providing respiratory support to the ELBWI. The extremely low birth weight infants pose a financial burden to the public health care sector and protocols should be in place on how to manage them.

Study limitations

This was a retrospective study of an already existing database. As such, there was missing data. During the study period, the unit was not offering delivery room NCPAP, and the time spent in the transitional unit while awaiting NCPAP was not documented. The study was conducted in a single centre tertiary referral, therefore cannot be generalised.

Conclusion

Our study shows that SRT and NCPAP are effective interventions in the management of RDS in ELBWI. Although the overall survival of ELBWI is still low, there is improved survival with implementation of respiratory support.

Timeous audits and research should be undertaken in all provinces in SA to assist in updating policies on ICU admission and management of ELBWI.

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Approved research protocol

University of the Witwatersrand

Department of Paediatrics and Child Health

Ventilatory support and surfactant use in extremely low birth weight infants over a decade at a tertiary hospital in Johannesburg, South Africa.

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TABLE OF CONTENTS:

1.Background

Premature infants weighing less than 1000g are a major contributor to neonatal mortality and morbidity. This increased mortality and morbidity is mainly attributed to respiratory distress syndrome (RDS), [1] which is primarily the disorder of pulmonary surfactant deficiency in immature lungs. [2,3] The immature lungs have decreased compliance which is likely to cause atelectasis. This in turn will lead to ventilation-perfusion mismatch, severe hypoxaemia, and hypercarbia. Furthermore, there is added risk of lung injury from mechanical ventilation. [2,3]

The alveolus is the primary site of gaseous exchange with the blood, and due to its spherical shape and small size it has a tendency to collapse.[2-4] Pulmonary surfactant is synthesized and secreted by the type II pneumocytes into the alveolar space.[3,4] Pulmonary surfactant increases the compliance of the lungs by reducing surface tension thus preventing atelectasis.[3,4] According to the study by Warren and Anderson, 60% of infants < 28 weeks gestation developed RDS, with an incidence of 30% and less than 5% in infants between 28 and 34 weeks gestation and above 34 weeks gestation, respectively.[5] Extremely low birth weight infants (ELBWI) are at greatest risk as the incidence of RDS and severity correlate inversely with gestational age.

Treatment of RDS begins antenatally with administration of maternal steroids to pregnant women who are at risk of preterm labour between 24 to 34 weeks gestation. Once the infant is born and has features of RDS clinically and/or radiologically, exogenous surfactant can be administered.

Exogenous surfactant therapy increases the surfactant storage pool in preterm infants (which is approximately 4-5mg/kg at birth compared to 100mg/kg in term infants) and improves pulmonary gas exchange until enough endogenous surfactant is released from the storage

pool.[1] Animal derived surfactants are the standard of care for RDS while synthetic surfactants are still under evaluation.[1]

The timing for administering exogenous surfactant is still under discussion. However, it was shown that early surfactant therapy reduced the need for intubation, [1, 2, 3,6] an important outcome in a resource limited centre. The techniques for administering surfactant have been changing over time, with more studies advocating for minimally invasive surfactant administration namely, the less invasive surfactant administration (LISA) or the minimally invasive surfactant therapy (MIST) which have been shown to reduce the need for mechanical ventilation and bronchopulmonary dysplasia(BPD).[1,7] This technique involves surfactant administration while the patient is spontaneously breathing and receiving non- invasive ventilation.

Since it was first described in 1971, nasal continuous positive airway pressure (NCPAP) has been widely used as a less invasive mode for respiratory support in the management of RDS. [1,2,3,7] NCPAP provides continuous positive pressure which helps to recruit collapsed or fluid filled alveoli, thus improving perfusion ventilation mismatch and increasing the functional residual capacity thereby improving oxygenation in the neonate. [1, 3, 7] The early use of NCPAP in premature infants reduces the need for surfactant replacement therapy (SRT) and mechanical ventilation. [7]

If a ventilator is required for respiratory support for the ELBWI, rapid extubation to NCPAP is preferable to prolonged ventilation due to the risk of lung injury leading to BPD. [1,7]

The Sustainable Development Goal (SDG) target 3 aims to reduce the neonatal mortality rate (NMR) to at least 12 per 1 000 live births in all countries by 2030. [8,9] The South African Demographic Health Survey (SADHS) reported a NMR of 21 per 1 000 live births in 2016 which is concerning as it is far above the rate of 12.6 per 1000 live births as reported by the

District Health Information System (DHIS).[10,11] An audit conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) by Ballot et al, revealed that the most common causes of death in the neonatal unit were prematurity (46.2%), intrapartum hypoxia (19.5%) and infection (17.2%), figures almost similar to those demonstrated by Perinatal Problem Identification Programme (PPIP) -an audit tool for evaluating the final neonatal cause of death and documents any avoidable causes in 2016.[12]According to the Saving Babies Report (which uses data from PPIP), 60% of premature deaths was accounted for by ELBWI (<1000g at birth)] which makes it a major contributing factor to NMR.[10,13] It was also noted that birth weight and gestational age were still the strongest predictors of survival in neonates. [12, 14, 15, 16] In a report from CMJAH, the survival rate of ELBWI between 2006/2007 and 2013 showed a marked improvement from 20.4% to 52.4% respectively.

This marked improvement in survival was attributed to the provision of surfactant and NCPAP to this weight category of neonates [14,15] In 2006 to 2010 Kalimba *et al.* carried out a study at CMJAH looking solely at infants weighing ≤900g and the survival rate was low at 26.5% with a mean birth weight 774g.[16] Kirsten *et al.* at Tygerberg Children's hospital in the Western Cape reported the survival rate of ELBWI to be 62.9% which is almost comparable to the 68% at Groote Schuur hospital also in the Western Cape in 2003/2005. [17, 18] It must be noted, however, that the infants in the above-mentioned studies were offered back-up mechanical ventilation for failed NCPAP, which was not applicable to the group from CMJAH.

Rationing of ventilatory support based on birth weight has been practiced widely in South Africa, due to resource limitations. Birth weight is used rather than gestational age as, in many instances, the gestational age is not well documented. In the early 2000s, the birth weight cut-off for any ventilatory support at CMJAH was 1000 grams. With the introduction of NCPAP into the unit in 2006, which was provided in the high care ward, neonates above 750 grams at birth were provided with surfactant and NCPAP. The cut-off for mechanical ventilation was

decreased to 900 grams. Neonates who did not qualify for ventilatory support were provided with warmth, intravenous fluids, supplemental oxygen, nutrition, and antibiotics. That policy has since been revised regarding surfactant therapy, NCPAP and ventilation, as infants above 800g are offered back up mechanical ventilation for failed NCPAP.

Over the 10 year period there were two major policy changes implemented at CMJAH neonatal unit. Firstly, surfactant and NCPAP were introduced for ELBWI weighing more than 750g around 2006/2007. The weight cut off for mechanical ventilation was reduced from 900g to 800 in 2014. In 2015 the unit tried to move away from birth weight altogether and offered all the ELBWI in good condition surfactant and NCPAP.

There is no consensus on what care to provide to the ELBWI as their care varies in different regions and countries. There are variable opinions by neonatologists towards the limit of viability worldwide. [19] Most developed countries use gestational age (GA) of 25 weeks as the cut off for treatment and resuscitation of infants below 25 weeks is seen as a futile effort leaving the decision to resuscitate the infants to the treating doctor and parents' wishes. [19-21]

In SA different provinces also have different protocols in the management of ELBWI. In the Western Cape, ELBWI weighing 500-650g are only eligible for NCPAP if inborn and outborn infants weighing 650-799g are eligible for transfer to a tertiary hospital on case by case basis.[22] Some centres in Kwa Zulu Natal advocate for palliative care for infants weighing less than 1000g if they are outborn.[23]

The mortality of ELBWI affects the U5MR negatively so care should be directed at changes in maternal and infant care practices. Once the infants are born, the treating doctor should be vigilant of the morbidities and measures should be put in place for prevention, early detection and intervention of those morbidities.

Surfactant replacement therapy, NCPAP and mechanical ventilation remain the mainstay of

therapy for RDS. The aim of this study is to review surfactant use and ventilatory support of ELBWI at CMJAH neonatal unit over a ten year period. We can use this data to inform policies on ICU admission and management of ELBWI.

2. Study Objectives:

1. To describe the types of ventilatory support and surfactant use during the study period and its effect on survival of ELBWI.
2. To describe the maternal and neonatal demographics and clinical characteristics (as per attached data collection sheets) during the study period.
3. To determine the survival of ELBWI by birth weight (using different weight categories: 400-499g, 500-599g,600-699g, 700-799g, 800-899g and 900-999g).
4. To determine if place of birth (inborn and outborn) affects outcome (survived or died) during the study period.

3. METHODS

Study design:

This will be a secondary analysis of an already existing database. This study will include ELBWI admitted to CMJAH neonatal unit from 01 January 2008 to 31 December 2017.

Inclusion criteria:

All EBLWI admitted to the CMJAH neonatal unit within 48 hours of birth will be included.

Exclusion criteria:

- Delivery room deaths as they would have died before admission to the neonatal unit

Variables

The maternal demographics and infant's information will be collected as per attached data collection sheet. Every variable will be entered in Excel for cleaning and storage.

4. Data Analysis

4.1. Data management

Secondary analysis of an existing database will be done. Data is collected by clinicians upon discharge or death of the infant using hospital records for the purpose of clinical audit and quality improvement. Data was managed using Microsoft Access (2006-2012) and Research Electronic Data Capture (REDCAP) [24] hosted by University of Witwatersrand subsequently. The collected data will be captured in a Microsoft Excel spreadsheet for data cleaning and coding purposes. Statistic programme SPSS version 25 IBM will be used for analysis.

4.2. Sample size

A review of the data base indicates that approximately 1500 ELBWI were admitted to the CMJAH neonatal unit over the study period.

4.3. Statistical analysis

Categorical variables will be reported as frequency and percentages while continuous variables will be reported as means with standard deviation or median with interquartile range (IQR) depending on distribution of data.

Chi square test will be used to compare categorical variables between groups. The paired t- test will be used to compare continuous variables with a normal distribution. Mann -Whitney test will be used for continuous variables that are not normally distributed. Mechanical ventilation, NCPAP and surfactant will be compared for survivors and non survivors using Chi square. Chi square will also be used to compare outcome (survived or died) for inborn and outborn infants.

A p-value of <0.05 will be considered as statistically significant.

5. Ethics

The protocol for this study will be submitted to the Postgraduate Committee of the University of Witwatersrand and Human Research Ethics Committee of the University of the Witwatersrand.

All data will be de-identified – i.e. name, surname, hospital number, date of birth, date of admission will all be removed prior to analysis.

6. Funding

Stationary R200

Printing R350

Transport from Chris Hani Baragwanath to CMJAH (18KM)-R1000 for 15 trips

All costs will be funded by investigator.

7. Timeline

Activity	July 2019	Aug 2019	Sep 2019	Oct 2019	Nov 2019	Dec 2019	Jan 2019	Feb 2020	Mar 2020	Apr 2020	May 2020	July 2020	Aug 2020
Literature review													
Preparing for protocol													
Protocol assessment													
Ethics application													
Data collection													
Data analysis													
Writing up													

8. Limitation

This is a retrospective study using data that is already collected with a possibility of missing data.

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Appendices

DATA COLLECTION SHEET

Study number:

INFANT'S DETAILS

Birth weight	
Gestational age	
Place of Birth	Inborn ☐ Out born ☐
Mode of delivery	NVD ☐ Caesarean section ☐
Gender	Male ☐ Female ☐
Apgar score	
Respiratory distress syndrome	Yes ☐ No ☐
Surfactant	Yes ☐ No ☐ If yes, number of doses
Mode of ventilation	NCPAP ☐ Conventional ventilation ☐
Patent ductus arteriosus	Yes ☐ No ☐
Chronic lung disease	Yes ☐ No ☐
Retinopathy of prematurity	Yes ☐ No ☐
Outcome	Discharged ☐ Demised ☐
Initial resuscitation	Yes No

Died within 12 hours of life	Yes No
Necrotising enterocolitis	Yes No
Length of hospital stay	
Congenital birth defect	Yes No
Neonatal sepsis	Yes No

MATERNAL DETAILS

Age	
Parity	
Antenatal care	Booked ☐ Unbooked ☐
Antenatal steroids	Yes ☐ No ☐
Multiple pregnancy	Yes ☐ No ☐
Attempted termination of pregnancy	Yes ☐ No ☐
Co morbidities	Hypertension Diabetes mellitus Syphilis HIV Chorioamnionitis

ABBREVIATIONS

Extreme low birth weight infant	ELBWI
Sustainable Development Goal	SDG
Perinatal Problem Identification Programme	PPIP
Charlotte Maxeke Johannesburg Academic Hospital	CMJAH
Rapid Mortality Surveillance	RMS
Vermont Oxford Network	VON
Neonatal mortality rate	NMR
SA Demographic Health Survey	SADHS
Nasal continuous positive airway pressure	NCPAP
SRT	Surfactant replacement therapy
District Health Information System	DHIS

SAMJ Author Guidelines

Manuscript preparation for South African Medical Journal

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, *full* affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g., 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g., µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counsellors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.

- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.

- Scans/photos showing a specific feature e.g., *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
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NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]

- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
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  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

  - Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

  - Provincial Gazettes:

  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

  - Acts:

  South Africa. National Health Act No. 61 of 2003.

  - Regulations to an Act:

  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

  - Bills:

  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

  - Green/white papers:

  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

  - Case law:

  Rex v Jopp and Another 1949 (4) SA 11 (N)

  Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

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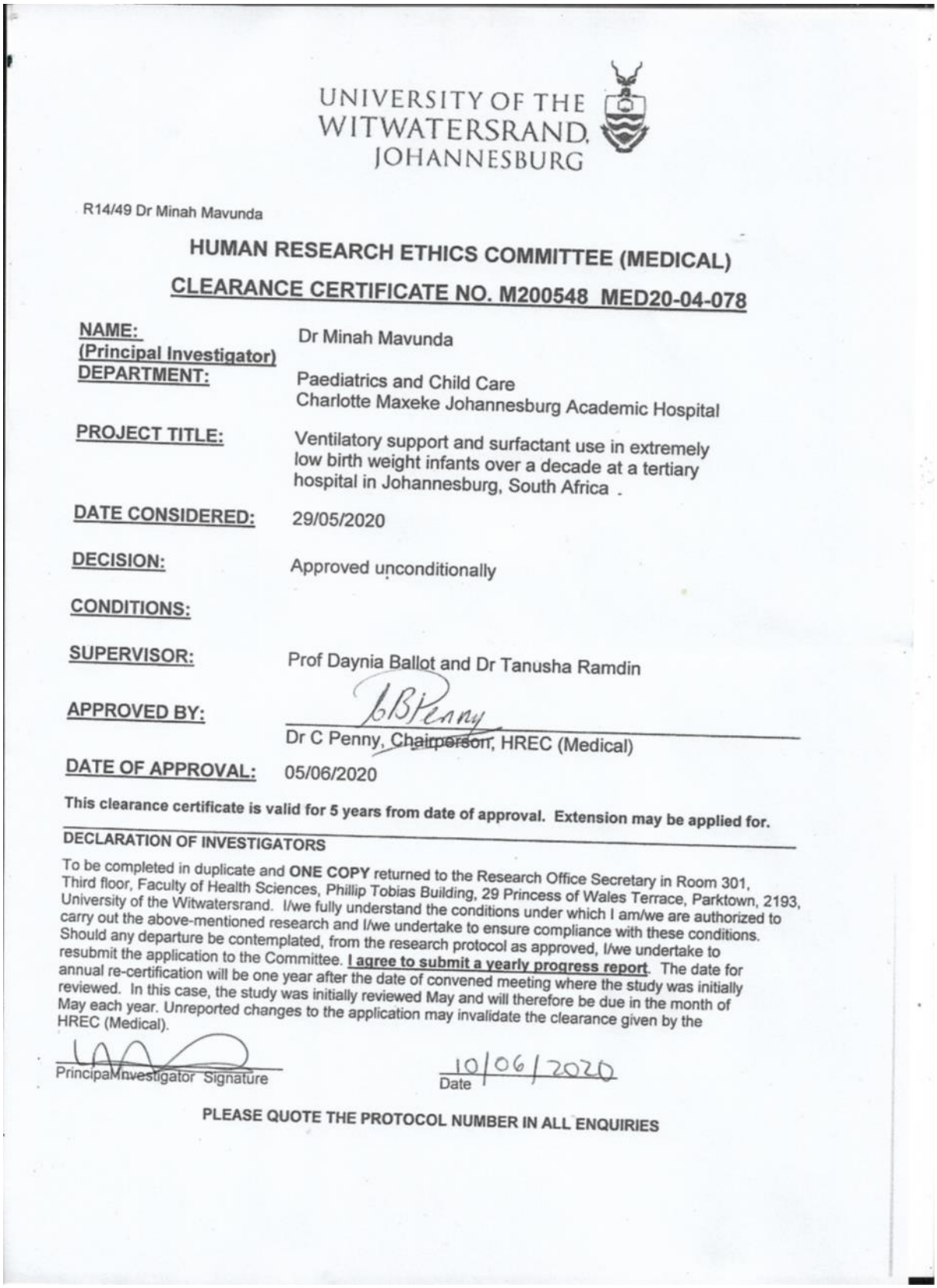

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Minah Mavunda

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200548 MED20-04-078

NAME: (Principal Investigator)	Dr Minah Mavunda
DEPARTMENT:	Paediatrics and Child Care Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Ventilatory support and surfactant use in extremely low birth weight infants over a decade at a tertiary hospital in Johannesburg, South Africa .
DATE CONSIDERED:	29/05/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot and Dr Tanusha Ramdin
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/06/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed May and will therefore be due in the month of May each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 10/06/2020

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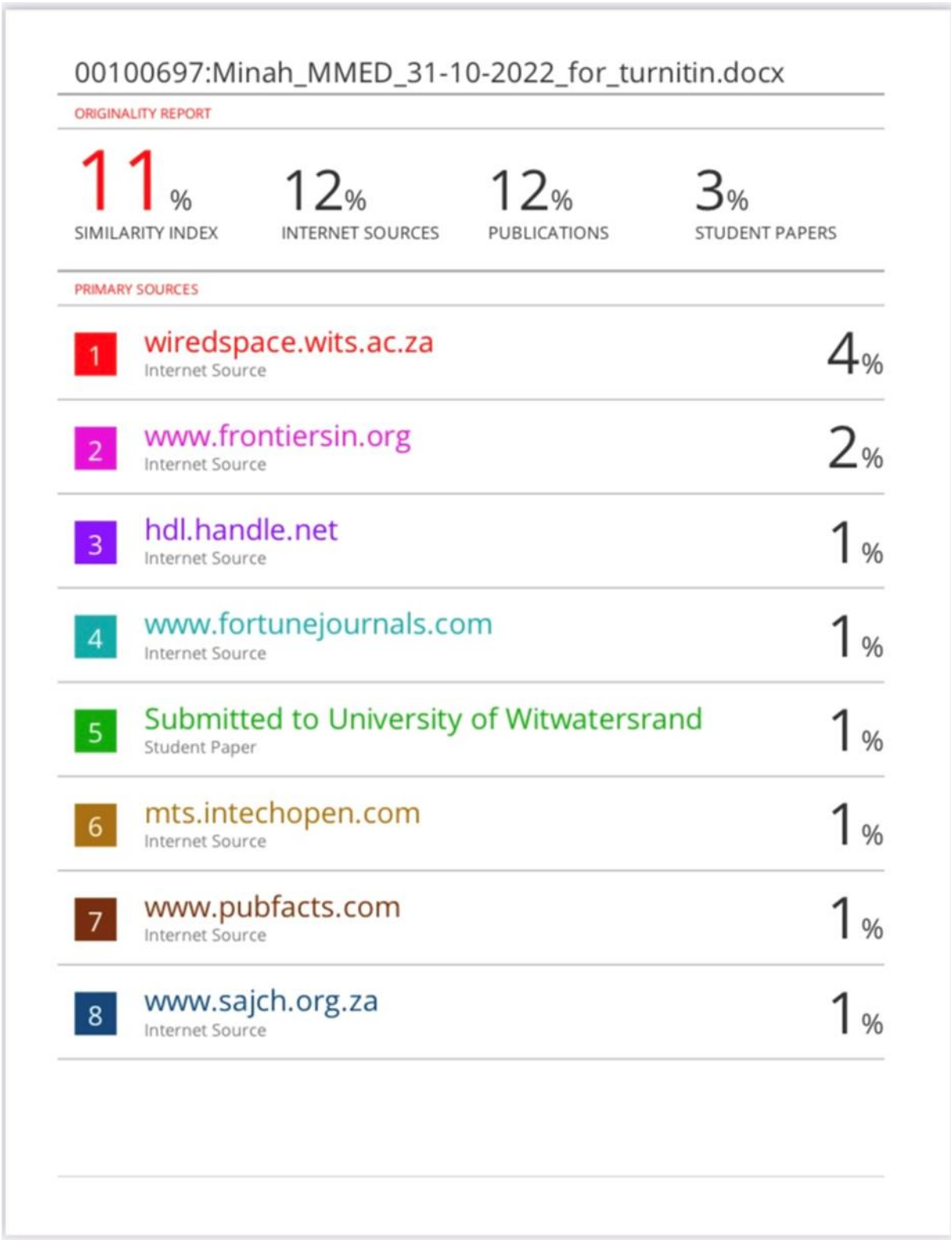

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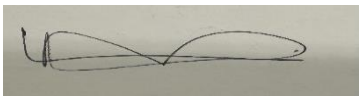
Signature: ___  Date: 27/04/2023