A Description of Premature and Ex-Premature Infants Admitted to the Paediatric Intensive Care Unit in the First Six Months of Life

By

Grace Mathew

MTHGRA005

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Faculty of Health Sciences

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Supervisor: Rossouw, B

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1. Declaration

I, Grace Thangam Mathew, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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2. Abstract (253 words)

Background: Prematurity is a major risk factor for morbidity and mortality in children. Rehospitalisation with paediatric intensive care unit (PICU) admission constitutes significant morbidity. There is a paucity of literature regarding rehospitalisations of premature infants in South Africa.

Objective: To describe the outcomes, clinical course and characteristics of premature infants admitted to a South African PICU, and to identify any predictors of mortality.

Methods: This prospective observational study analysed unplanned PICU admissions of premature and ex-premature infants in the first six months of life, over a six-month period. The primary and secondary outcomes were mortality and length of PICU stay, respectively. Data were analysed using standard descriptive and inferential statistics.

Results: 29 infants (65% male; median (IQR) birth weight (BW) and gestational age (GA) 1715 (1130 - 2340) g and 32 (29 - 34) weeks respectively) in 33 admissions were included. Five (17.2%) infants died in PICU.

Apnoea (39.4%), respiratory failure (24.2%) and shock (24.2%) were the commonest reasons for PICU admission, secondary to pneumonia (33.3%), sepsis (27.3%) and meningitis (12.1%). 72.4% of infants were mechanically ventilated and 48.3% received blood transfusions.

Higher revised Paediatric Risk of Mortality (PIM2) score ($p = 0.03$), inotrope use ($p < 0.0001$), longer duration of mechanical ventilation ($p = 0.03$), and cardiac arrest in PICU ($p < 0.0001$) were associated with mortality on univariate analysis with no independent predictors of mortality.

Conclusion: Infections leading to apnoea, respiratory failure and shock are common indications for PICU readmission in premature infants. Mechanical ventilation and blood transfusion were frequently required.

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4. List of abbreviations

BW	Birth weight
BPD	Bronchopulmonary dysplasia
CLD	Chronic lung disease
ELBW	Extremely low birth weight
EPI	South African Extended Programme on Immunisation
g	Grams
GA	Gestational age
Hb	Haemoglobin
HREC	Human Research Ethics Committee
HIV	Human Immunodeficiency Virus
ICU	Intensive care unit
IQR	Interquartile range
IVH	Intraventricular haemorrhage
kg	Kilograms
L1	Level 1 or district hospital
L2	Level 2 or regional hospital
L3	Level 3 or tertiary hospital
LBW	Low birth weight
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
PICU	Paediatric intensive care unit
PIM2	Revised Paediatric Index of Mortality Score
RCWMCH	Red Cross War Memorial Children's Hospital
RSV	Respiratory syncytial virus
RTHB	Road to Health Book
SD	Standard deviation
SMR	Standardised mortality ratio
VLBW	Very low birth weight
USA	United States of America
w	Weeks
WAZ	Weight-for-age z-score
WHO	World Health Organization
WHZ	Weight-for-length/height z-score

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6. CHAPTER ONE: BACKGROUND AND LITERATURE REVIEW

Background

Prematurity is a major risk factor for morbidity and mortality. According to the World Health Organization (WHO), preterm birth complications is the leading cause of death in children under-5 years[1]. In a recent review of mortality in children under-5 years of age in the Metro West geographical service area of the Western Cape Province, prematurity was found to be the third leading cause of death; it accounted for 9.3% of all deaths[2].

Care of the premature new-born is an ever-evolving paediatric discipline[3]. There have been dramatic advancements in the knowledge and interventions related to care of any premature infant. Survival is not only a possibility, but most often the expectation, in many situations once considered to be futile[4]. However, the risk in these cases is that a premature infant may survive with significant morbidity. The consequence of this may mean increased demands on the health care system and family in the future.

Research into the outcome of this growing group of surviving premature infants in low to middle income countries is limited; particularly when specifically considering those infants who become seriously ill and require readmission in to a neonatal or paediatric intensive care unit (PICU). It is critically important to have data that accurately shows the burden of disease within this population, as well as any risk factors that are identifiable so as to identify those infants who are especially susceptible to increased morbidity and/or mortality.

Red Cross War Memorial Children's Hospital (RCWMCH) functions as the tertiary level hospital within the Cape Town West Metro District for all children beyond the neonatal period. The study was based at this center as it is the only PICU within the public sector for this district. Currently there are no published studies reflecting data from South Africa as well as the Sub-Saharan district.

As per the World Health Organisation, the classification of premature and underweight infants is as follows[5]:

- <28 weeks (w): extremely preterm
- 28 to <32 weeks: very preterm
- 32 to <37 weeks: moderate to late preterm

- <1000 grams (g): extremely low birth weight (ELBW)
- 1000 g to <1500 g: very low birth weight (VLBW)
- 1500 g to <2500 g: low birth weight (LBW).

Objectives

The objectives of this literature review were:

1. To describe the impact of prematurity on paediatric morbidity, in terms of rehospitalisations and mortality in the research setting globally
2. To describe the most common illnesses that require rehospitalisations in this population
3. To review data on the risk factors associated with rehospitalisations and mortality in premature infants
4. To review data on the protective factors associated with decreased rehospitalisation and mortality in premature infants
5. To review available data related to rehospitalisation requiring admission to an intensive care unit (ICU), and any information regarding diagnosis, length of stay and requirement of mechanical ventilation

Literature Search Strategy and Search Results

Pubmed searches were made from inception until February 2018 using the following keywords

1. Premature birth AND Patient readmission
2. Infant, premature AND Patient readmission

A total of 102 articles were found using the above search strategies, 13 of these studies were identified in more than both searches.

The search was not limited in any way. Certain additional articles recommended by the supervisor or experts in the field were included in the review. A total of 106 articles were reviewed, of which 26 articles are referenced in this literature review. The majority of the articles were published during or after 2010, but 10 articles from before this period were included.

6.1 Rehospitalisation Rate

Several studies have been done over the years looking at the rehospitalisation rate to any ward after discharge from the birth admission (Table 1). Most of these studies have been done in the first world setting. Interestingly, despite the increased resources available in these countries, the rehospitalisation rate remains high.

In 2003, a review focused on ELBW infants was published and specifically considered rehospitalisation rates by 2 years corrected age through different time periods[6]. It showed that despite medical advances, these rates were found to increase; in 1980-82%, 52% of the infants required rehospitalisation at least once, in 1991-1992, 62% and in 1997, 66%.

Several studies have addressed rehospitalisation rates over various periods of time and most showed the majority of the rehospitalisations occur in the first year of life, even as high as 49% of infants born before 32 weeks gestational age (GA) in Finland[7]. In Austria, a study found that 40% of infants born before 32 weeks GA required rehospitalisation, and almost half of these infants required multiple admissions within the first year[8].

Two studies were done where children were followed up for 18 years and both found that premature infants required more rehospitalisations than term infants. In Australia, extremely preterm infants required an average of 6 admissions over 18 years, compared with <2 admissions for term infants[9]. 62% of VLBW infants required rehospitalisation when followed up until the age of 18 years in Israel[10].

A study done in India looked specifically at ELBW infants until the age of two corrected years[11]. The focus of this study was growth, and rehospitalisations over this period was a secondary outcome. 44% of these infants required rehospitalisations within the first year of life. This is in keeping with studies done in higher income settings[7,8].

Table 1 Rehospitalisation Rate				
Study	**Setting and participants**	**Study Type**	**Outcomes**	**Findings**
Elder et al.[12] N=538 1999	GA <33 w at birth. Australia	Prospective cohort study	Rehospitalisations for the first year of life corrected age	0.01%: died 42%: one or more readmissions
Escobar et al.[13] N=6054 1999	All neonates discharged from a neonatal intensive care unit (NICU). United States of America (USA)	Retrospective cohort study	Rehospitalisations in the first two weeks after discharge	2.72%
Doyle et al.[6] N=196 2003	ELBW infants randomly selected. First world countries	Review article	Comparison of rehospitalisation rate over three distinct time periods (1980-1982, 1991-1992, 1997) at 2 years corrected age	1980-1982: 52% 1991-1992: 62% 1997: 66%
Smith et al.[14] N=1597, 238 with bronchopulmonary dysplasia (BPD) 2004	GA <33 w, infants with BPD compared to those without. USA	Retrospective cohort study	Rehospitalisations in the first year of life	BPD: 49% No BPD:23%
Brissaud et al.[15] 2005	GA ≤ 33 w, discharged from neonatal unit. France	Retrospective cohort study	Rehospitalisations in the first year of life in 1997 and 2002	1997: 29.1% 2002: 30.1%
Escobar et al.[16] n=677 2006	GA 30-<35 w discharged from a neonatal unit. USA	Retrospective cohort study	Rehospitalisations within 3 months of discharge	11.3%
Tomashek et al.[17]. N=25324 2006	Live-born singleton infants, vaginally delivered, hospital stay <2 nights USA	Retrospective cohort study	Rehospitalisation rate and diagnosis over first 28 days of life	Late preterm: 3.5% Term: 2%

Underwood et al.[18] 2007	GA <36 w USA	Prospective cohort study	Rehospitalisation rate, diagnosis, length of stay over first year of life	15% within first year of life
Korvenranta et al.[7] n=2148 2009	GA <32 w, Birth weight (BW) <1501 g Finland	Retrospective cohort study	Prevalence of prematurity-related disorders and rehospitalisations over the first 3 years of life	1st year: 49.3% 2nd year: 28% 3rd year: 20.9%
Luu et al.[19] n=254 2010	GA ≤28/40 w Canada	Prospective cohort study	Neurodevelopmental outcomes and health care use until 18 months corrected age	23-25 w GA: 57% 26-28 w GA: 49%
Tseng et al.[20]. N=18421 2010	Any preterm GA, any LBW infant Taiwan	Prospective cohort study	Rehospitalisation within 31 days from discharge	13.5%
Ambalavanan et al.[21] N=3787 2011	BW <1000 g USA	Retrospective analysis	Rehospitalisation before 18-22 month corrected age Rehospitalisation for respiratory causes before 1 year chronological age	Before 18-22 months corrected age: 45% Before 1 year chronological age: 14.7%
Seki et al.[22] n=609 2011	GA <34 w Japan	Prospective cohort study	Rehospitalisation by 3 months and by 1 year	GA 22-25 w 3 months: 10.4% 1 year: 26.9% GA 26-34 w 3 months: 2.8% 1 year: 7.4%
Ralser et al.[8] N=377 2012	GA <32 w Austria	Prospective cohort study	Rehospitalisations within first 2 years of life	1st year: 40.1% 2nd year: 24.7%
Kuzniewicz et al. [23] 2013	GA >31 w USA	Review article	Rehospitalisations and emergency department visits in first 30 days after discharge	31-33 w: 2.9% 34-36 w: 8% 37-38 w: 6.8% 39 w +: 3.3%
Vrijlandt et al.[24] n=2112	GA <32 w compared to GA 32-36 w and GA ≥37 w The Netherlands	Prospective cohort study	Rehospitalisations for respiratory problems and respiratory symptoms until the age of 5 years	<32 w: 17% 32-36 w: 6% ≥ 37 w: 3%
Moyer et al.[25] n=1861 2014	GA 34-36 w USA	Prospective cohort study	Rehospitalisations within 28 days of birth	3.6%

Mukhopadhyay et al.[11] n=79 2014	ELBW <1000 g India	Prospective cohort study	Followed up until corrected age of 2 years Primary: proportion of underweight Secondary: proportion of stunting, microcephaly, wasting, mortality and morbidity during first year of age	Rehospitalisation in first year: 44% (35 of 79) 21 children once, 9 twice, 5 three times Deaths: 11% (9 of 79)
Slimings *et al.*[9] N= 721702 2014	All births Australia	Retrospective cohort study	Rehospitalisations until 18 years of age after birth discharge	*First 28 days:* 4.4% Moderate and late preterm: 8.9% each of above *After the neonatal period*, extremely preterm infants had the highest rate of readmissions until the age of 18; >50% in the first year and >60% in from the second to fifth years of life. *Over 18 years* Extremely preterm: 6 admissions Term: <2 admissions
Lee *et al*.[26] N=2351 2015	GA <33 w Korea	Retrospective cohort study	Followed up for an average of 425 days Outpatient, clinic, emergency department visits and hospitalisations	33.6% Of 1322 rehospitalisation events, 113 (8.5%) required mechanical ventilation 14 infants died (0.6%), 11 of which occurred in the first year

Hong *et al.*[27] N=3322 2016	GA <32 w at birth. Australia	Retrospective cohort study	Rehospitalisations in the three years following discharge for respiratory causes and respiratory syncytial virus (RSV) - related rehospitalisations	0.91%: died 63%: at least one rehospitalisation 37.7%: respiratory rehospitalisation 11.8%: RSV-related rehospitalisation Most of these deaths and readmissions occurred within the first year post discharge.
Taylor *et al.*[28] N=142 2016	GA <29 w USA	Retrospective cohort study	Rehospitalisations within first two years of life	Rehospitalisations At 1 year: 42% (18% multiple rehospitalisations) At 2 years: 45% 7 died (0.05%)
Kuint *et al.*[10] N=6385 2017	VLBW ≤1500 g Israel	Observational study	Rehospitalisations within 18 years from birth discharge	62%

6.2 Diagnosis at Rehospitalisation

There have been many studies that address the common reasons that premature infants require rehospitalisation (Table 2). Most seem to indicate that respiratory disorders and infections are the commonest cause of rehospitalisations in premature infants.

Jaundice, infection and feeding issues were often the reason for rehospitalisations within the first month of life[13,17,23]. But infants followed up for a longer time were noted to have very different reasons for rehospitalisation.

Various studies done from 1999[12] to 2016[28] found respiratory illnesses to be the commonest reason for diagnosis. In 2010, researchers in Canada[19] found that 63% of their infants born before 28 w GA required admission for respiratory illnesses when followed up until 18 months corrected age.

Doyle *et al.*[6] reviewed several studies specifically considering ELBW infants in the first world setting. As mentioned previously, this studied focused on rehospitalisations until two years corrected age over three separate time periods: 1980-1982, 1991-1992, and 1997. Throughout all three time periods, medical reasons for rehospitalisations were found to be

more common, in particular respiratory rehospitalisations. Infection with RSV was also found to be a common cause of respiratory illness requiring rehospitalisation[18,27].

In India, ELBW infants were followed up until two years corrected age. This is the only study done in a low-income setting[11]. Infections were found to be the reason for rehospitalisation in the majority of cases (15% sepsis, 15% pneumonia, 11% acute gastroenteritis, 6% bronchiolitis). There was a high rate of loss to follow-up during the study and this may have resulted in an underestimate of mortality and rehospitalisations.

Surgical admissions for repair of inguinal hernias were also one of the more common reasons for rehospitalisation[12,14].

Table 2 Diagnosis at Rehospitalisation

Study	Setting and participants	Study Type	Outcomes	Findings
Elder *et al.*[12] n=538 1999	GA <33 w at birth. Australia	Prospective cohort study	Rehospitalisations for the first year of life corrected age	83.5% of rehospitalisations: medical, almost half of these acute respiratory illnesses 16.5% of rehospitalisations: surgical, majority for repair of inguinal hernia
Escobar et. al[13]. n=6054 1999	All neonates discharged from a NICU. USA	Retrospective cohort study	Rehospitalisations in the first two weeks after discharge	Jaundice and feeding issues
Doyle *et al.*[6] n=196 2003	ELBW infants randomly selected. First world countries	Review article	Comparison of rehospitalisation rate over three distinct time periods (1980-1982, 1991-1992, 1997) at 2 years corrected age	Medical admissions more common, particularly respiratory rehospitalisations
Smith *et al.*[14] n=1597, 238 with BPD 2004	GA <33 w, infants with BPD compared to those without. USA	Retrospective cohort study	Rehospitalisations in the first year of life	Respiratory diagnoses and hernia repair
Brissaud *et al*.[15] 2005	GA ≤ 33 w, discharged	Retrospective cohort study	Rehospitalisations in the first year of life in 1997 and 2002	Respiratory disease

	from neonatal unit. France			
Tomashek *et al.*[17] n=25324 2006	Live-born singleton infants, vaginally delivered, hospital stay <2 nights USA	Retrospective cohort study	Rehospitalisation rate and diagnosis over first 28 days of life	Jaundice and infection
Jain *et al.*[29] n=279 2006	GA 34-36 w presenting to emergency department USA	Observational study	Admission diagnosis and rehospitalisation over first 31 days of life	The six most common diagnosis accounted for 70% of the admissions. Gastrointestinal (20.4%), respiratory (15.8%), jaundice (12.2%), infectious (8.2%), feeding problem (7.5%), fever 6.8%)
Underwood *et al.*[18] 2007	GA <36 w USA	Prospective cohort study	Rehospitalisation rate, diagnosis, length of stay in the first year of life	Acute respiratory diseases most frequent, RSV most common pathogen
Luu *et al.*[19] n=254 2010	GA ≤28/40 w Canada	Prospective cohort study	Neurodevelopmental outcomes and health care use until 18 months corrected age	63%: respiratory illness, 16% surgery, 11% gastrointestinal/nutrition problems
Ambalavanan *et al.*[21] n=3787 2011	BW <1000 g USA	Retrospective analysis	Rehospitalisation before 18-22 month corrected age Rehospitalisation for respiratory causes before 1 year chronological age	45.4%: respiratory diagnosis 20.5%: surgery 6% infection
Ralser *et al.*[8] n=377 2012	GA <32 w Austria	Prospective cohort study	Rehospitalisations within first 2 years of life	Respiratory disorders most common
Kuzniewicz *et al.* [23] 2013	GA >31 w USA	Review article	Rehospitalisations and emergency department visits in first 30 days after discharge	31-33 w: Infection, respiratory disorders 34 w +: Infection, jaundice
Mukhopadhyay *et al.*[11] n=79 2014	ELBW <1000 g India	Prospective cohort study	Followed up until corrected age of 2 years Primary: proportion of underweight Secondary: proportion of	Anaemia 19% Sepsis 15% Pneumonia 15% Acute gastroenteritis 11% Bronchiolitis 6%

			stunting, microcephaly, wasting, mortality and morbidity during first year of age	Laser treatment of retinopathy of prematurity 6% Inguinal hernia 12% Fever 6% Deaths: 9 children (11%) Sepsis 6, pneumonia 3
Lee *et al.*[26] n=2351 2015	GA <33 w Korea	Retrospective cohort study	Followed up for an average of 425 days Outpatient, clinic, emergency department visits and hospitalisations	18.4% respiratory problems
Hong *et al.*[27] n=3322 2016	GA <32 w at birth. Australia	Retrospective cohort study	Rehospitalisations in the three years following discharge for respiratory causes and RSV-related rehospitalisations	37.7%: respiratory rehospitalisation 11.8%: RSV-related rehospitalisation

6.3 Risk Factors for Rehospitalisation

It is vitally important to identify factors that increase the likelihood of premature infants requiring rehospitalisations. This could potentially have a significant impact on the follow-up required for infants identified as high risk.

Many studies have been done to try to accurately determine these risk factors (Table 3). Male sex[8,12,14,16,20,27] was consistently found to be associated with an increased rate of rehospitalisations.

Lower gestational age at birth and lower birth weight[14,15,18,20] were both frequently found to result in a higher frequency of rehospitalisations. A birth weight below 1000 g was specifically noted to be associated with increased rates of rehospitalisations[15,20].

Chronic lung disease (CLD) and bronchopulmonary dysplasia also leads to increased frequency of rehospitalisations[8,12,15].

Kuint *et al*.[10] followed VLBW infants for 18 years of life and assessed whether having certain morbidities were associated with an increased requirement for rehospitalisations. They specifically looked at the following morbidities: necrotising enterocolitis (NEC), necrotising enterocolitis with surgery, intraventricular haemorrhage (IVH) grades 3-4, periventricular

leukomalacia, bronchopulmonary dysplasia and retinopathy of prematurity stages 3-4. They found that those with necrotising enterocolitis requiring surgery and grades 3-4 IVH were at highest risk. Of note, they found that the presence of one of these morbidities increased the risk of rehospitalisation by 2.7-fold, the presence of two morbidities by 2.46-fold, and three or more by 4.22-fold excess risk. The presence of morbidities could potentially have a significant effect on the needs for rehospitalisations in an already susceptible group of patients.

Table 3 Risk Factors for Rehospitalisation

Study	Setting and participants	Study type	Outcomes	Findings
Elder et al.[12] n=538 1999	GA <33 w at birth. Australia	Prospective cohort study	Rehospitalisations for the first year of life corrected age	Medical rehospitalisations: aboriginal race, male sex and CLD Surgical rehospitalisations: male sex, lower GA, severe HMD, severe CLD, birthweight <10th centile
Escobar et. al[13]. n=6054 1999	All neonates discharged from a NICU. USA	Retrospective cohort study	Rehospitalisations in the first two weeks after discharge	Highest rate of rehospitalisation in those with GA 33 to 36 w
Smith et al.[14] n=1597, 238 with BPD 2004	GA <33 w, infants with BPD compared to those without. USA	Retrospective cohort study	Rehospitalisations in the first year of life	No BPD: Lower GA, lower BW, male sex, longer initial NICU hospitalisation, longer duration of respiratory support, presence of NEC and IVH
Brissaud et al.[15] 2005	GA ≤ 33 w, discharged from neonatal unit. France	Retrospective cohort study	Rehospitalisations in the first year of life in 1997 and 2002	BW <1000 g, CLD, GA <28 w
Escobar et al.[16] n=677 2006	GA 30-<35 w discharged from a neonatal unit USA	Retrospective cohort study	Rehospitalisations within 3 months of discharge	Male sex

Underwood et al.[18] 2007	GA <36 w USA	Prospective cohort study	Rehospitalisation rate, diagnosis, length of stay over first year of life	GA <25 w BW <1000 g
Luu et al.[19] n=254 2010	GA ≤28/40 w Canada	Prospective cohort study	Neurodevelopmental outcomes and health care use until 18 months corrected age	BPD, severe brain injury, use of home oxygen or apnoea monitor, older chronological age at neonatal discharge.
Tseng et al.[20] N=18421 2010	Any preterm GA, any LBW infant Taiwan	Prospective cohort study	Rehospitalisation within 31 days from discharge	Male, BW <1000g, congenital abnormalities, lung disease
Ralser et al.[8] n=377 2012	GA <32 w Austria	Prospective cohort study	Rehospitalisations within first 2 years of life	1st year: CLD, male sex, smoking in pregnancy 2nd year: CLD
Lee et al.[26] n=2351 2015	GA <33 w Korea	Retrospective cohort study	Followed up for an average of 425 days Outpatient, clinic, emergency department visits and hospitalisations	GA <30 w
Hong et al.[27] n=3322 2016	GA <32 w at birth Australia	Retrospective cohort study	Rehospitalisations in the three years following discharge for respiratory causes and RSV-related rehospitalisations	<u>High respiratory rehospitalisations</u>: male gender, requiring intubation resuscitation at birth, culture-proven systemic infection, maternal indigenous status, major congenital anomalies, higher days of assisted ventilation, severe BPD requiring home oxygen RSV <u>High RSV-related rehospitalisations</u>: Lower gestational age at birth, severe BPD requiring home oxygen, indigenous background, assisted ventilation
Taylor et al.[28] n=142 2016	GA <29 w USA	Retrospective cohort study	Rehospitalisations within first two years of life	Rehospitalisations: number of respiratory infections, inhaled steroid use at 1 year PICU Rehospitalisations: pulmonary hypertension in NICU, prolonged oxygen use, increasing

				number of respiratory infections Multiple rehospitalisations: increasing number of respiratory infections and feeding problems
Kuint et al.[10] n=6385 2017	VLBW ≤1500 g Israel	Observational study	Rehospitalisations within 18 years from birth discharge	Younger maternal age at delivery, maternal ethnicity, lower GA, multiple birth, male sex, small for gestational age, delivery room resuscitation, congenital malformations VLBW with any major morbidity, particularly NEC requiring surgery and grades 3-4 IVH

6.4 Protective Factors that Reduce Rehospitalisations

Five studies specifically noted factors that reduced the likelihood of rehospitalisations (Table 4). Two of the studies looked closely at rehospitalisations within the first few months of life.

In Taiwan[20], all infants who were identified as either premature or any low birth weight were followed up prospectively for the first 31 days post discharge. A neonatal length of stay less than 35 days was seen as a protective factor. This may be a marker for less morbidity within the neonatal period leading to a shorter hospital stay at birth.

On the other hand, preterm infants born between 34 to 36 weeks GA (moderate preterm) in USA required fewer rehospitalisations if they were born via caesarean section or if they had a longer neonatal length of stay[25]. This may point to a concern that although moderate preterm infants are often not as unwell at birth, they may still have significant morbidity associated with prematurity. A longer initial hospital stay to identify these morbidities and adequately manage them may reduce their risk for rehospitalisations. Three of these studies followed the infants for one year or longer.

In Australia[27], 3322 infants born before 32 weeks were noted to have fewer rehospitalisations over the first three years of life if they received exogenous surfactant in the birth hospitalisation.

Interestingly, two of these studies identified breast milk ingestion as protective factors. In 1999, Elder *et al.*[12] found this in Australia in infants born before 33 weeks GA. Interestingly, 17 years later, in USA, Taylor *et al.*[28] found the same in premature infants born before 29 weeks GA. This is valuable information as encouraging breast milk feeds, sometimes via expressed milk, is an inexpensive and safe intervention that should probably be a priority in all neonatal units globally.

Table 4 Protective Factors that Reduce Rehospitalisations

Study	Setting and participants	Study type	Outcomes	Findings
Elder *et al.*[12] n=538 1999	GA <33 w at birth. Australia	Prospective cohort study	Rehospitalisations for the first year of life corrected age	Medical readmission: Breastfeeding
Tseng *et al.*[20] N=18421 2010	Any preterm GA, any LBW infant Taiwan	Prospective cohort study	Rehospitalisation within 31 days from discharge	Shorter neonatal length of hospital stay (<35 days)
Moyer *et al.*[25] n=1861 2014	GA 34-36 w USA	Prospective cohort study	Rehospitalisations within 28 days of birth	Delivery via caesarean section with longer initial hospital stay
Hong *et al.*[27] n=3322 2016	GA <32 w at birth. Australia	Retrospective cohort study	Rehospitalisations in the three years following discharge for respiratory causes and RSV-related rehospitalisations	Respiratory hospitalisations: exogenous surfactant administration RSV-related rehospitalisations: older maternal age at birth
Taylor *et al.*[28] n=142 2016	GA <29 w USA	Retrospective cohort study	Rehospitalisations within first two years of life	Breastmilk ingestion

6.5 PICU Rehospitalisation

In 2010, Gunville *et al.*[30] reviewed PICU hospitalisations for acute respiratory illness in all children under the age of two years at a tertiary centre in Denver, Colorado (Table 5). There were 271 infants included in the study and 30% of these children were preterm; 17% early preterm (<32 w GA) and 12% late preterm (32 - <36 w GA). The most common diagnosis among all these children was lower respiratory tract infection.

They found that preterm infants had a longer length of stay in the PICU and used more hospital resources during their hospitalisation.

In a prospective study in 16 different centres in the USA, Mourani[31] *et al.* identified 512 infants who were born ≤34 weeks, with a birth weight between 500 and 1250 g who required mechanical ventilation within the first 48 hours of life (Table 5). These infants had been recruited for another randomised controlled trial and were followed up until the age of four and a half years. 18.7% (96 of 512) of these children required rehospitalisation to a paediatric ICU, and most of these were in the first year of life (75 of 96). The average length of stay in the PICU was 13.6% days per rehospitalisation. Three of these 96 children demised.

47 of the 96 children who were admitted a PICU required mechanical ventilation for an average of 11.6 days. There was an increased risk for rehospitalisation into a PICU in male infants and those with intracranial haemorrhage at discharge from the birth hospitalisation.

Two years later, Taylor *et al.*[28] found that 10% of infants born before 29 weeks GA were rehospitalised to a PICU within the first two years of life (Table 5). The average age of admission was at the age of 13 months. Some identified risk factors were the use of inhaled steroids, diuretics or diuretics at the age of one year.

Table 5 PICU Rehospitalisation

Study	Setting and participants	Study type	Outcomes	Findings
Gunville *et al.*[30] n=271 2010	Children admitted to PICU less than 2 years of age with acute respiratory illness USA	Retrospective cohort study	Diagnosis, length of stay, hospital charges	Most common diagnosis: lower respiratory tract infection. Preterm infants: longer PICU length of stay, utilised more hospital resources, incurred higher hospital charges compared with term infants.
Mourani *et al.*[31] n=512 2014	GA ≤34 w BW 500-1250 g <48h old Required mechanical ventilation USA	Prospective cohort study of patients who had been involved in a randomised controlled trial at birth using inhaled nitric	Hospital readmissions and outpatient resource use until 4.5 years age	Rehospitalisations: 57.8% (296) of total ICU rehospitalisations: 18.7% (96 of 512) of total- 75 of these in the first year of life. Average of 13.6 days ICU days per admission

		oxide vs a placebo		Mechanical ventilation during rehospitalisations: 9.1%, (47 of 512) Average of 11.6 days on mechanical ventilation 3 deaths Male sex and the presence of intracranial haemorrhage at discharge from birth hospitalisations were risk factors associated with ICU rehospitalisation
Taylor *et al.*[28] n=142 2016	GA <29 w USA	Retrospective cohort study	Rehospitalisations within first two years of life	10% ICU rehospitalisations, average age: 13 months Risk factors: pulmonary hypertension in NICU prolonged oxygen use, increasing number of respiratory infections. The use of diuretics/inhaled steroids/oxygen at 1 year

Summary

Many studies have been done focused on readmissions in premature infants, most of these in the first world setting. Various studies done from the 1990s[6] until 2017[10] have shown that premature infants have a high rate of rehospitalisation after discharge. The highest frequency of rehospitalisations were generally in the first year of life, as high as 49% in infants born before 32 weeks GA in Finland[7]. In India, 44% of ELBW infants required rehospitalisations within the first year of life[11]. The increased rate of rehospitalisations persists until 18 years. In Australia, extremely preterm infants required an average of 6 admissions (term infants <2 admissions)[9] and in Israel, 62% of VLBW infants required rehospitalisation[10].

Within the first month of life, jaundice, infection and feeding issues were often the reason for rehospitalisations [13,17,23]. But as premature infants grow up, respiratory illnesses are the commonest reason for readmission [6,12,19,28]. Infection with respiratory syncytial virus was often associated with respiratory illness requiring rehospitalisation[18,27]. In India, infections

(sepsis, pneumonia and acute gastroenteritis) lead to rehospitalisation in the majority of cases in ELBW infants in the first year of life [11].

Male sex[8,12,14,16,20,27], CLD/BPD[8,12,15], lower gestational age at birth and lower birth weight[14,15,18,20] increased the risk of rehospitalisations, particularly a birth weight below 1000 g[15,20]. Kuint *et al.*[10] found that the presence of any morbidity associated with prematurity increased the rate of rehospitalisation in VLBW infants until 18 years of age in Israel.

Interestingly, two studies identified breast milk ingestion as protective factors to decrease the risk of rehospitalisations[12,28]. Despite medical advances, breast milk remains a critical target for reducing morbidity in premature infants.

Acute respiratory illnesses have consistently been found to be the most common reason for readmission into ICU, in particular, lower respiratory tract infection[30]. In 16 centres in USA[31], premature infants had a high rate of rehospitalisations (18.7%) and required prolonged ICU stays with an average of 13.6 days per admission. Most of these admissions were in the first year of life.

References for Background and Literature Review

1. *Children: reducing mortality.* Wkly Epidemiol Rec, 2014. **89**(38): p. 418-20.

2. Reid, A.E., M.K. Hendricks, P. Groenewald, et al., *Where do children die and what are the causes? Under-5 deaths in the Metro West geographical service area of the Western Cape, South Africa, 2011.* S Afr Med J, 2016. **106**(4): p. 51.

3. Shah, P.S., *Neonatal Intensive Care - The Only Constant Is Change.* N Engl J Med, 2017. **376**(7): p. 694-696.

4. Lassi, Z.S., P.F. Middleton, C. Crowther, et al., *Interventions to Improve Neonatal Health and Later Survival: An Overview of Systematic Reviews.* EBioMedicine, 2015. **2**(8): p. 985-1000.

5. Blencowe, H., S. Cousens, D. Chou, et al., *Born too soon: the global epidemiology of 15 million preterm births.* Reprod Health, 2013. **10 Suppl 1**: p. S2.

6. Doyle, L.W., G. Ford, and N. Davis, *Health and hospitalisations after discharge in extremely low birth weight infants.* Seminars in Neonatology, 2003. **8**(2): p. 137-145.

7. Korvenranta, E., L. Lehtonen, M. Peltola, et al., *Morbidities and hospital resource use during the first 3 years of life among very preterm infants.* Pediatrics, 2009. **124**(1): p. 128-134.

8. Ralser, E., W. Mueller, C. Haberland, et al., *Rehospitalization in the first 2 years of life in children born preterm.* Acta Paediatr, 2012. **101**(1): p. e1-5.

9. Slimings, C., K. Einarsdottir, R. Srinivasjois, et al., *Hospital admissions and gestational age at birth: 18 years of follow up in Western Australia.* Paediatr Perinat Epidemiol, 2014. **28**(6): p. 536-544.

10. Kuint, J., L. Lerner-Geva, G. Chodick, et al., *Rehospitalization Through Childhood and Adolescence: Association with Neonatal Morbidities in Infants of Very Low Birth Weight.* J Pediatr, 2017. **188**: p. 135-141 e2.

11. Mukhopadhyay, K., D. Louis, G. Mahajan, et al., *Longitudinal growth and post-discharge mortality and morbidity among extremely low birth weight neonates.* Indian Pediatr, 2014. **51**(9): p. 723-726.

12. Elder, D.E., R. Hagan, S.F. Evans, et al., *Hospital admissions in the first year of life in very preterm infants.* J Paediatr Child Health, 1999. **35**(2): p. 145-150.

13. Escobar, G.J., S. Joffe, M.N. Gardner, et al., *Rehospitalization in the first two weeks after discharge from the neonatal intensive care unit.* Pediatrics, 1999. **104**(1): p. e2.

14. Smith, V.C., J.A. Zupancic, M.C. McCormick, et al., *Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia.* J Pediatr, 2004. **144**(6): p. 799-803.

15. Brissaud, O., F. Babre, L. Pedespan, et al., *Rehospitalization of very preterm infants in the first year of life. Comparison of 2 groups: 1997 and 2002.* Arch Pediatr, 2005. **12**(10): p. 1462-1470.

16. Escobar, G.J., M.C. McCormick, J.A. Zupancic, et al., *Unstudied infants: outcomes of moderately premature infants in the neonatal intensive care unit.* Arch Dis Child Fetal Neonatal Ed, 2006. **91**(4): p. F238-44.

17. Tomashek, K.M., C.K. Shapiro-Mendoza, J. Weiss, et al., *Early discharge among late preterm and term newborns and risk of neonatal morbidity.* Semin Perinatol, 2006. **30**(2): p. 61-68.

18. Underwood, M.A., B. Danielsen, and W.M. Gilbert, *Cost, causes and rates of rehospitalization of preterm infants.* J Perinatol, 2007. **27**(10): p. 614-619.

19. Luu, T.M., F. Lefebvre, P. Riley, et al., *Continuing utilisation of specialised health services in extremely preterm infants.* Arch Dis Child Fetal Neonatal Ed, 2010. **95**(5): p. F320-325.

20. Tseng, Y.H., C.W. Chen, H.L. Huang, et al., *Incidence of and predictors for short-term readmission among preterm low-birthweight infants.* Pediatr Int, 2010. **52**(5): p. 711-717.

21. Ambalavanan, N., W.A. Carlo, S.A. McDonald, et al., *Identification of extremely premature infants at high risk of rehospitalization.* Pediatrics, 2011. **128**(5): p. e1216-25.

22. Seki, K., S. Iwasaki, H. An, et al., *Early discharge from a neonatal intensive care unit and rates of readmission.* Pediatr Int, 2011. **53**(1): p. 7-12.

23. Kuzniewicz, M.W., S.J. Parker, A. Schnake-Mahl, et al., *Hospital readmissions and emergency department visits in moderate preterm, late preterm, and early term infants.* Clin Perinatol, 2013. **40**(4): p. 753-775.

24. Vrijlandt, E.J., J.M. Kerstjens, E.J. Duiverman, et al., *Moderately preterm children have more respiratory problems during their first 5 years of life than children born full term.* Am J Respir Crit Care Med, 2013. **187**(11): p. 1234-1240.

25. Moyer, L.B., N.K. Goyal, J. Meinzen-Derr, et al., *Factors associated with readmission in late-preterm infants: a matched case-control study.* Hosp Pediatr, 2014. **4**(5): p. 298-304.

26. Lee, J.H., Y.S. Chang, C. Committee on Data, et al., *Use of Medical Resources by Preterm Infants Born at Less than 33 Weeks' Gestation Following Discharge from the Neonatal Intensive Care Unit in Korea.* J Korean Med Sci, 2015. **30 Suppl 1**: p. S95-S103.

27. Hong, T., S. Bolisetty, B. Bajuk, et al., *A population study of respiratory rehospitalisation in very preterm infants in the first 3 years of life.* J Paediatr Child Health, 2016. **52**(7): p. 715-721.

28. Taylor, J.B., M.A. Go, M.F. Nyp, et al., *Rehospitalization in Infants Born < 29 Weeks' Gestation during the First 2 Years of Life: Risk Assessment.* Am J Perinatol, 2016. **33**(1): p. 24-33.

29. Jain, S. and J. Cheng, *Emergency department visits and rehospitalizations in late preterm infants.* Clin Perinatol, 2006. **33**(4): p. 935-945; abstract xi.

30. Gunville, C.F., M.K. Sontag, K.A. Stratton, et al., *The scope and impact of early and late preterm infants admitted to the PICU with respiratory illness.* J Pediatr, 2010. **157**(2): p. 209-214 e1.

31. Mourani, P.M., J.P. Kinsella, G. Clermont, et al., *Intensive care unit readmission during childhood after preterm birth with respiratory failure.* J Pediatr, 2014. **164**(4): p. 749-755 e3.

7. CHAPTER TWO: PUBLICATION-READY MANUSCRIPT

7.1 Title page

A Description of Premature and Ex-Premature Infants Admitted to the Paediatric Intensive Care Unit in the First Six Months of Life

Grace Mathew, [1]* MBBCh (WITS) DCH (SA) FC Paed (SA); Beyra Rossouw, [1] MBChB DTM MSc MMed(Paed) Certificate Critical Care(Paed); Brenda Morrow[1] PhD (UCT); PG Dip Health Res Ethics (US); BSc Physiotherapy (UCT)

[1] Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town, South Africa

*Corresponding author: G Mathew (MTHGRA005@myuct.ac.za)

Research was performed at the Paediatric Intensive Care Unit, Red Cross War Memorial Children's Hospital, Cape Town, South Africa

Keywords: Premature Infant, Patient Readmission, Intensive Care Units, South Africa

7.2 Abstract

Background: Prematurity is a major risk factor for morbidity and mortality in children. Rehospitalisation with paediatric intensive care unit (PICU) admission constitutes significant morbidity. There is a paucity of literature regarding rehospitalisations of premature infants in South Africa.

Objective: To describe the outcomes, clinical course and characteristics of premature infants admitted to a South African PICU, and to identify any predictors of mortality.

Methods: This prospective observational study analysed unplanned PICU admissions of premature and ex-premature infants in the first six months of life, over a six-month period. The primary and secondary outcomes were mortality and length of PICU stay, respectively. Data were analysed using standard descriptive and inferential statistics.

Results: 29 infants (65% male; median (IQR) birth weight (BW) and gestational age (GA) 1715 (1130 - 2340) g and 32 (29 - 34) weeks respectively) in 33 admissions were included. Five (17.2%) infants died in PICU.

Apnoea (39.4%), respiratory failure (24.2%) and shock (24.2%) were the commonest reasons for PICU admission, secondary to pneumonia (33.3%), sepsis (27.3%) and meningitis (12.1%). 72.4% of infants were mechanically ventilated and 48.3% received blood transfusions.

Higher revised Paediatric Risk of Mortality (PIM2) score ($p = 0.03$), inotrope use ($p < 0.0001$), longer duration of mechanical ventilation ($p = 0.03$), and cardiac arrest in PICU ($p < 0.0001$) were associated with mortality on univariate analysis with no independent predictors of mortality.

Conclusion: Infections leading to apnoea, respiratory failure and shock are common indications for PICU readmission in premature infants. Mechanical ventilation and blood transfusion were frequently required.

7.3 Introduction

Prematurity is a major risk factor for morbidity and mortality. According to the World Health Organisation (WHO), preterm birth complications are the leading cause of death in children under-5 years[1]. In the Metro west geographical service area of the Western Cape Province, South Africa, prematurity was reported to be the third leading cause of death; accounting for 9.3% of all under-five deaths in the region[2]. There have been dramatic advancements in the knowledge and care of premature infants, with associated improvements in survival, even in cases which would previously have been considered futile. These interventions include the use of incubators, surfactant and continuous positive airway pressure[3]. However, these premature infants may survive with significant morbidity[4], and associated increased demands on the health care system and family in the future.

Studies conducted in well-resourced countries have identified premature infants as being at high risk of requiring readmission to hospital[5,6], with those readmitted to the neonatal or paediatric intensive care unit (PICU) being at increased risk of poor clinical outcome (prolonged PICU stay and mortality) compared to the general PICU population[7]. Male sex [5,8-12], chronic lung disease/bronchopulmonary dysplasia [8,11,13], lower gestational age (GA) at birth and lower birth weight (BW)[5,9,13,14] have been reported to be associated with increased risk of rehospitalisations, particularly a birth weight below 1000 grams (g)[5,13]. Kuint *et al.*[15] found that the presence of any morbidity associated with prematurity increased the rate of rehospitalisation in very low birth weight infants (VLBW) until 18 years of age in Israel. Breastfeeding has been identified as a protective factor[8,16] reducing the likelihood of rehospitalisation.

Acute respiratory illnesses, particularly lower respiratory tract infections, have consistently been reported to be a common reason for readmission into ICU[17]. Across 16 centres in the United States of America[7], premature infants had a high rate of rehospitalisations (18.7%) and required prolonged ICU stays with an average of 13.6 days per admission. Most of these admissions were in the first year of life. There is limited data on the characteristics, outcomes and impact on the healthcare system of infants requiring readmission to PICU in low and

middle-income countries. A study done in India found that infections (sepsis, pneumonia and acute gastroenteritis) lead to rehospitalisation in the majority of cases in extremely low birth weight (ELBW) infants in the first year of life[18]. Forty four percent of their cohort of ELBW infants were rehospitalised and 11% of these died within the first year of life. It is particularly important to identify infants at increased risk of poor clinical outcomes in resource-constrained environments as they may require closer surveillance and support. This study aims to describe the incidence, demographics, clinical course and outcomes of premature infants admitted to a South African PICU, following initial hospital discharge, within the first six months of life. Currently there are no published studies reflecting data from South Africa or the broader Sub-Saharan region.

7.4 Methods

Study design and participants

This was a prospective observational study of all premature infants below the age of six months, admitted to the PICU at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, South Africa, from 1 May 2016 to 31 October 2016. All planned admissions, such as those admitted following elective surgery, were excluded from the study. The Human Research Ethics Committee (HREC) at University of Cape Town granted ethical approval for this study (approval no. HREC REF: 103/2016) and informed consent was taken from participants' parents or legal guardians.

Setting

RCWMCH is the only paediatric tertiary level (L3) hospital within the Cape Town Metro West geographical service area in Western Cape, with a wide scope of subspecialty services offered. The PICU at RCWMCH is a 22-bed unit providing the only intensive care unit (ICU) for paediatric admissions within the public health sector in the region. The neonatal services within this district are offered by one L3 hospital (Groote Schuur Hospital) several secondary level (L2) hospitals (New Somerset Hospital, Mowbray Maternity Hospital and George Hospital) and district level (L1) hospitals and multiple maternity obstetric units. Tygerberg Hospital offers tertiary level services to the Metro East geographical service area. Usually, once an infant is discharged from the neonatal services, any rehospitalisations required would

be to a paediatric unit, including RCWMCH. During the period of data collection, the staffing of the PICU in terms of the nurses and doctors remained fairly stable.

Definitions

As per the WHO[19], the classification of premature and underweight infants is as follows:

- <28 weeks: extremely preterm
- 28 to <32 weeks: very preterm
- 32 to <37 weeks: moderate to late preterm
- <1000 g: extremely low birth weight (ELBW)
- 1000 g to <1500 g: very low birth weight (VLBW)
- 1500 g to <2500 g: low birth weight (LBW).

Gestational age of any infant is determined using several options which include antenatal ultrasonography, calculations based on last menstrual period and scoring based on physical examination of the neonate, such as the Ballard Score. A correlation between foot length and gestational age is possible but was not used during the period prior to data collection for this study. An early ultrasound done up to 23 completed weeks is considered to be the most accurate estimate of GA. Soon after birth, the GA of a child is determined by the attending clinician based on one or more of the above-mentioned assessments.

Data collection

Daily checks were made to identify patients who fulfilled inclusion criteria. Once informed consent was obtained from the parent or legal guardian, medical records and "Road to Health" books (RTHB) of each infant were reviewed.

Birth weight, gestational age at birth, gender, mode of delivery, and date of birth was recorded for each participant. The corrected age and chronological age were then calculated for each child. The RTHB was reviewed to collect data regarding initial hospital length of stay following birth, morbidities, discharge weight, immunization status as well as human immunodeficiency virus (HIV) status.

HIV status was classified as uninfected, exposed but uninfected, infected not on treatment, and infected on treatment.

Immunisation status was based on the expected immunisations that each child should have received at the time of admission based on the South African Extended Programme on Immunisation (EPI).

The weight of the infant on the day of admission to PICU was used to assess the child's growth since discharge from the neonatal unit. The nutritional status of each child was determined using weight-for-age (WAZ) and weight-for-height/ length (WHZ) z-scores after correction for prematurity, calculated using the "zanthro" function of Stata®/IC 13.0 statistical software. The WHO 2007 UK term and preterm growth charts were used for reference (Birth: British 1990 Growth Reference, reanalysed 2009; Postnatal: WHO Child Growth Standards; 4-20 years: British 1990 Growth Reference). A child was assessed as growing slowly if they had gained weight since the time of discharge from the neonatal unit but had not followed the trend according to the previously mentioned growth charts.

During the PICU admission, data regarding initial reason for admission, revised Paediatric Index of Mortality (PIM2) score, diagnosis on discharge, mode of feeding (breastmilk, formula feeds or mixed feeding), length of stay, respiratory support, transfusion of blood and blood products and unexpected interventions such as surgery or dialysis was collected. Laboratory results related to haemoglobin (Hb), microbiological and viral studies were also collected. The PIM2 score is designed for use in any PICU and uses various physiologic variables to assist with mortality risk assessment at initial admission to PICU[20]. It is used as a benchmark to assess performance in any PICU and has been validated for use in the PICU at RCWMCH[21]. A standardised mortality rate (actual mortality over predicted mortality) below one is a good reflection as it shows that fewer patients die than those predicted using the PIM2 score.

Data Analysis and Main Outcome Measures

Data were tested for normality using the Shapiro Wilks W test. Descriptive data are presented as n (%) for categorical variables and either median (interquartile range, IQR) or mean (standard deviation (SD)) according to distribution for continuous variables. Inferential statistics were conducted using Chi-square tests (or yates corrected Chi- square as appropriate) for categorical variables and continuous data were compared using Mann-Whitney U or t- tests for independent variables. The primary outcome measure was mortality

and secondary outcome was length of PICU stay. Data identified as being significantly associated with mortality on univariate analysis were entered into a backward stepwise binary logistic regression model to determine any independent predictors. A *p*-value < 0.05 was considered significant for all tests. Statistica 13 (StatSoft Inc, USA) was used for statistical analysis.

7.5 Results

During the six-month study period there were 584 admissions to the PICU, of which 33 (5.7%) were unplanned admissions of 29 premature-born infants (males, n=19; 65.5%). Within the same period, there were a total of 43 deaths in PICU, five (11.6%) of whom were patients included in this study (Table 1).

Patient characteristics and outcomes

Characteristics and outcomes of the 29 included infants are presented in Table 1. One (3.4%) child had a GA of 24 weeks; 11 (37.9%) were very preterm and 17 (58.6%) were moderate to late preterm infants. The majority (51.7%) of infants had spent more than four weeks in the neonatal unit.

Eight (27.6%) infants were discharged from the neonatal unit with a known morbidity, the commonest of these being a late infection (10.3%) during the birth hospitalisation. One of the infants had a grade 3-4 intraventricular haemorrhage, and another had necrotising enterocolitis during the neonatal admission. More than half of the infants (51.7%) admitted to the PICU had a neonatal length of stay exceeding four weeks.

Of the 29 infants requiring readmission to PICU, nine (31%) were noted to have a WAZ or WHZ z-score below -2 at the time of readmission or had lost weight since discharge from the neonatal unit. These children were classified as malnourished (Table 1). Two of these children were on formula feeds. None of the children were HIV infected.

Table 1: Admission Characteristics and Outcomes (n=29)

	All	Died	Survived	p value
Male Gender	19 (65.5%)	4 (13.8%)	15 (51.7%)	0.5
Delivery by caesarian section	8 (27.6%)	1 (3.4%)	7 (24.1%)	0.7

BW median (IQR) (g)	1715 (1130 - 2340)	1800 (1180 - 2410)	1667.5 (1115 - 2320)	0.8
GA median (IQR)	32 (29 - 34)	32 (28 – 34)	32.5 (29 - 34)	0.9
PIM2 Score median (IQR) (%)	4.13 (1.36 - 7.56)	13.17 (7.56 - 62.23)	3.8 (1.08 - 5.53)	0.03
Length of stay in neonatal unit				
None	4 (13.8%)	2 (6.9%)	2 (6.9%)	0.4
<4 days	2 (6.9%)	0	2 (6.9%)	
4 - <7 days	2 (6.9%)	0	2 (6.9%)	
1 - 2 weeks	5 (17.2%)	1 (3.4%)	4 (13.8%)	
2 - 4 weeks	1 (3.4%)	0	1 (3.4%)	
>4 weeks	15 (51.7%)	2 (6.9%)	13 (44.8%)	
Presence of Morbidities	8 (27.6%)	2 (6.9%)	6 (20.7%)	0.4
Corrected Age on PICU admission				
35 - < 37 weeks	7 (24.1%)	1 (3.4%)	6 (20.7%)	0.8
37 - < 40 weeks	7 (24.1%)	2 (6.9%)	5 (17.2%)	
40 weeks to <1	6 (20.7%)	1 (3.4%)	5 (17.2%)	
1 to <3 months	5 (17.2%)	1 (3.4%)	4 (13.8%)	
≥ 3 months	4 (13.8%)	0	4 (13.8%)	
Actual Age on PICU admission				
<1 month	8 (27.6%)	2 (6.9%)	6 (20.7%)	0.7
1 - <2 months	7 (24.1%)	1 (3.4%)	6 (20.7%)	
2 - <4 months	10 (34.5%)	2 (6.9%)	8 (27.6%)	
4 - 6 months	4 (13.8%)	0	4 (13.8%)	
Admission weight				
<2 kg	6 (20.7%)	0	6 (20.7%)	0.4
2 -< 4 kg	19 (65.5%)	5 (17.2%)	14 (48.3%)	
4 - <6 kg	3 (10.3%)	0	3 (10.3%)	
≥6 kg	1 (3.4%)	0	1 (3.4%)	
Growth since discharge				
Growing well	14 (48.3%)	3 (10.3%)	11 (37.9%)	0.5
Growing slowly	6 (20.7%)	0	6 (20.7%)	
Malnourished or weight loss	9 (31%)	2 (6.9%)	7 (24.1%)	
Time since Neonatal Unit discharge				
<1 weeks	2 (6.9%)	0	2 (6.9%)	0.1
1 - 2 weeks	3 (10.3%)	0	3 (10.3%)	
>2 weeks - 1 month	8 (27.6%)	4 (13.8%)	4 (13.8%)	

>1 - <2 months	10 (34.5%)	1 (3.4%)	9 (31%)	
≥2 months	6 (20.7%)	0	6 (20.7%)	
Immunisations not up to date	11 (37.9%)	0	11 (37.9%)	0.1
Feeding				
Breast	21 (72.4%)	4 (13.8%)	17 (58.6%)	0.7
Formula	5 (17.2%)	1 (3.4%)	4 (13.8%)	
Mixed	3 (10.3%)	0	3 (10.3%)	
HIV Status				
HIV positive	0	0	0	0.3
HIV exposed, but negative	4 (13.8%)	0	4 (13.8%)	
HIV unexposed	25 (86.2%)	5 (17.2%)	20 (69%)	
ICU days				
<1 day	2 (6.9%)	0	2 (6.9%)	0.1
1 day	3 (10.3%)	2 (6.9%)	1 (3.4%)	
2 - 3 days	8 (27.6%)	1 (3.4%)	7 (24.1%)	
4 - 7 days	8 (27.6%)	0	8 (27.6%)	
>7 days	8 (27.6%)	2 (6.9%)	6 (20.7%)	
Mechanical ventilation	21 (72.4%)	5 (17.2%)	16 (55.2%)	0.1
Mechanical ventilation days				
none	8 (27.6%)	0	8 (27.6%)	0.03
<1 day	2 (6.9%)	0	2 (6.9%)	
1 day	3 (10.3%)	2 (6.9%)	1 (3.4%)	
2 - 3 days	3 (10.3%)	1 (3.4%)	2 (6.9%)	
4 - 7 days	9 (31%)	0	9 (31%)	
>7 days	4 (13.8%)	2 (6.9%)	2 (6.9%)	
Received inotropes	6 (20.7%)	5 (17.2%)	1 (3.4%)	< 0.0001
Blood transfusion	14 (48.3%)	4 (13.8%)	10 (34.5%)	0.1
PICU intervention (surgery or dialysis)	8 (27.6%)	3 (10.3%)	5 (17.2%)	0.1
Cardiac arrest	5 (17.2%)	5 (17.2%)	0	< 0.0001

The most common reason for PICU admission was found to be apnoea (Table 2). At the time of discharge, respiratory illnesses were the cause of 48.2% of the admissions and infectious illnesses were associated with 86.2% of the admissions to PICU (Table 2).

The vast majority of admissions secondary to infective causes had no identified microbial diagnosis; one infant was found to have a growth of *Group B streptococcus* on blood culture. One child was treated as a presumed *Bordetella pertussis* infection. Although this is a vaccine preventable infection, this child had received three doses of the EPI-funded *Bordetella pertussis* vaccination. Respiratory syncytial virus (RSV) was isolated in four (13.8%%) patients, three of whom were diagnosed with respiratory tract infections. Two of these patients were admitted during the RSV season and none of the 29 infants received palivizumab.

Table 2: Reason for Admission and Discharge Diagnosis (n=33 admissions)

Reason for Admission	
Apnoea	13 (39.4%)
Respiratory failure	8 (24.2%)
Septic shock	5 (15.2%)
Hypovolaemic shock	3 (9.1%)
Cardiac arrest	2 (6.1%)
Other	2 (6.1%)
Discharge Diagnosis	
Pneumonia	11 (33.3%)
Bronchiolitis	1 (3%)
Upper airway obstruction	2 (6.1%)
Sepsis	9 (27.3%)
Meningitis	4 (12.1%)
Other	6 (18.2%)

Course

Invasive ventilation

Twenty- four of the 33 admissions (72.7%) were intubated and mechanically ventilated during the course of the PICU stay. Table 1 presents total duration of PICU stay and mechanical ventilation for the included infants.

Procedures

One child required emergency dialysis and seven infants underwent surgery during their PICU admission (Table 3).

Table 3: Surgical procedures and outcomes (n=7)

Infants admitted immediately following emergency surgery		
Procedure	**Indication**	**Outcome**
Laparotomy	Incarcerated inguinal hernia	Survived
Tracheostomy (n=2)	Upper airway obstruction (n=2)	Survived (n=2)
Laparotomy	Abdominal distension and feed intolerance	Survived
Emergency surgery performed during PICU stay		
Procedure	**Indication**	**Outcome**
Patent ductus arteriosus ligation	Cardiac failure	Survived
Laparotomy	Incarcerated hernia	Died
Removal of ventriculoperitoneal shunt and placement of external ventricular drain	Ventriculitis	Survived

Inotropes

Six of the 33 admissions (18.2%) received inotropes and five of these infants died. None of the infants who did not receive inotropes died ($p < 0.0001$; Table 1).

Blood transfusions

Fourteen (48.3%) infants received blood transfusions (Table 1). Infants who received blood transfusions had lower median (IQR) birth weight (1170 (1000 - 1715) g vs. 2300 (1620 - 2410) g; $p = 0.01$) and younger median (IQR) gestational age (29.5 (28 – 32) weeks vs 33 (31 – 36) weeks; $p = 0.02$) compared to those who did not receive transfusions. The median haemoglobin for which a transfusion was administered was 8.5 g/dL. The timing of these blood transfusions following admission to PICU is unknown.

Cardiac arrests

Five of the infants admitted to the PICU were successfully resuscitated following at least one cardiac arrest in the PICU (Table 4). Despite this, all of these infants eventually died in PICU. One of these events occurred in an infant during a second admission to the PICU.

Table 4: Cardiac arrests in PICU (n=5)

Gestational age (weeks)	Birth weight (grams)	Reason for admission
28	800	Septic shock
28	1180	Septic shock
32	1800	Apnoea
34	2490	Hypovolaemic shock
36	2410	Septic shock

Outcomes

Five (17.2%) of the 29 infants died in PICU. The standardised mortality ratio (actual/mean predicted mortality, SMR) was 1.39.

Higher PIM2 score on admission; a longer period of mechanical ventilation; receipt of inotropes and cardiac arrest were associated with PICU mortality on univariate analysis (Table 1). However, none of these associations were found to be independent predictors of mortality on multiple regression analysis. There was no difference in gestational age or birth weight between infants who died vs. those who survived (Table 1; $p > 0.4$).

7.6 Discussion

This is the first study performed in sub-Saharan Africa looking at rehospitalisations of premature infants in any setting. Over the six-month period, 29 infants were admitted to the PICU. Although premature infants in the first six months of life formed only 5.7% of the total number of admissions in the study period, 11.6% of the deaths in the unit were infants included in this study.

A higher PIM2 score on admission was associated with death during PICU admission (p=0.03), and the SMR of 1.39 shows that the actual mortality was greater than the predicted mortality. As the PIM2 score is calculated on admission to PICU, it is potentially a useful indicator for early identification of those infants who have an increased risk of mortality. The PIM2 score has been shown to accurately predict mortality internationally and has been validated for use in the PICU at RCWMCH[21].

All of the children who had an initial successful resuscitation following a cardiac arrest eventually demised in PICU. All of these infants also required inotropes in PICU while none of the infants who did not receive inotropes died.

The receipt of inotropes ($p < 0.0001$), a longer period of mechanical ventilation days ($p = 0.03$) and cardiac arrest in PICU ($p < 0.0001$) were all associated with mortality on univariate analysis. However, with multiple regression analysis, none of these factors were found to be independent predictors of mortality. No correlation was found between birth weight or gestational age and mortality ($p \geq 0.4$).

Apnoea and respiratory failure were identified as the reason for admission in 39.4% and 24.2%, respectively, of admissions to PICU. This is unsurprising as the literature review showed similar findings[11,12,14,22]. Shock was found to be another common reason for admission, specifically septic shock in 15.2% and hypovolaemic shock in 9.1% of the admissions. On discharge, infections were noted to be the final diagnosis in 75.8% of admissions. These infections include pneumonia (33.3%), sepsis (27.3%), meningitis (12.1%) and bronchiolitis (3%), which is in keeping with the findings of Mukhopadhyay *et al*.[18] in a study done in India. RSV infection was isolated in three (9.1%) of the patients diagnosed with respiratory tract infection. Underwood *et al*[14]. and Hong *et al*[12]. both found that RSV-related illness was a significant cause for rehospitalisation.

In this study group, 54.5% of the PICU admissions were for four days or longer, with 21.2% of these lasting longer than 7 days. In 2014, Mourani *et al*[7]. reported that in the first four and a half years of life, 49% of the 96 premature infants admitted to PICU required mechanical ventilation for an average of 11.6 days. In our study, intubation and mechanical ventilation was required in a greater percentage (72.4%) of admissions, but only four were ventilated for more than seven days. Gunville *et al*[17]. report that premature infants generally have a longer length of stay in PICU and utilise more hospital resources than infants born at term. Although this study does not have the capacity to show similar findings, it does suggest that premature infants utilise a significant amount of hospital resources.

Infants of a lower gestational age at birth or those with a lower birth weight were significantly more likely to require blood transfusion ($p \leq 0.05$). This was also found by Mukhopadhyay *et al.*[18] in infants born weighing less than 1000 g at birth. It may be beneficial to routinely prescribe haematinics to all premature infants on discharge from the neonatal unit as iron supplementation has been found to decrease the risk of developing iron deficiency anaemia in preterm infants[23].

The majority of the infants were male, in keeping with the findings of Tseng *et al*.[5] and several other studies[9,12,24]. Seventeen (58.6%) of the infants weighed 1500 g or more at birth and seventeen (58.6%) of the infants were born at or after 32 weeks of gestation. Although one study[10] reported similar findings, most literature suggests that a lower GA or birth weight increases the risk of rehospitalisation[5,13-15,25]. Our findings suggest that moderate to late preterm infants are also susceptible to the consequences of prematurity, in this setting and should therefore receive the same care and follow-up as extremely preterm infants.

More than half of the infants admitted to the PICU had an initial neonatal length of stay longer than four weeks, although only 27.6% of infants were noted to have significant morbidity on neonatal unit discharge.

Thirty eight percent of infants in our study were missing immunisations. This is concerning in terms of public health and preventative health care. Although *Bordetella pertussis* infection was presumed in one case, the affected infant had received three doses of the vaccine for *Bordetella pertussis*. No other EPI administered vaccine-preventable causes of admission were identified. RSV prophylaxis (palivizumab)is not routinely available in the study region, despite being recommended during RSV season for children born at a gestational age below 36 weeks, who are younger than 6 months [26]. Only one of the three children affected by RSV-related respiratory illnesses would have fulfilled the criteria to receive RSV prophylaxis, if it were available. Therefore one of the 33 (3.0%) admissions was potentially avoidable had palivizumab been available in the neonatal units during the study period.

It was fairly reassuring to find that all the infants were HIV uninfected on admission, including those at risk for Mother-To-Child transmission, and the vast majority were receiving exclusive breastmilk feeds. Despite this, only 48.3% of the infants were noted to be growing well and 31% of the infants had either lost weight since discharge from the neonatal unit or were categorized as malnourished. Most of the infants were admitted more than a month after discharge from the neonatal unit. Early identification and timeous intervention in infants that are not growing well is required to optimise the health and well-being of all premature infants.

Improved access to antenatal care and family planning services to decrease the incidence of prematurity has to become, and remain, a priority for all those involved in the provision of health care. Health promotion with regard to breastfeeding support, regular visits to primary health care facilities for monitoring of growth and wellness, as well as promoting immunisations provided through the EPI program needs to become a major focus of the care of all infants, and in particular, those born preterm.

Study Limitations

This study has several limitations. Data was collected only on premature infants over a period of six months. The lack of a control group increases the likelihood of confounding bias within this study. The small study sample as well as the short study period affects the validity of the findings of this study. The small study sample may be a reflection of data collection occurring when the incidence of respiratory viral infections were possibly fewer. The information related to the neonatal admission was mostly found in the RTHB and some details regarding the neonatal admission may have been incomplete, resulting in potential information bias. This study also has not included any infants who may have been rehospitalised in a PICU in another hospital or other districts in South Africa.

7.7 Conclusions and recommendations

Over a six-month period, 5.7% of the total admissions and 11.6% of the deaths in PICU were of premature infants within the first six months of life, with a SMR >1. Factors associated with mortality on univariate analysis were: PIM2 score, receipt of inotropes, duration of

mechanical ventilation and cardiac arrest in PICU; however independent predictors of mortality could not be identified in this small cohort. These findings suggest that premature infants utilise a considerable proportion of PICU resources and are at increased risk of serious illness and mortality. Further research is required to clarify the extent of resource utilisation, morbidity and overall mortality in this population of infants.

Prematurity remains a significant risk factor for morbidity, and further studies are required to gain insight into the true burden of disease associated with prematurity in Southern Africa, including the healthcare resource consumption outside the PICU. Preventative health care is a priority, specifically in terms of decreasing the incidence of premature deliveries as well as improving health care for all mothers, infants and children.

7.8 References for Publication-ready Manuscript

1. WHO, *Children: Reducing mortality.* Wkly Epidemiological Rec., 2014. **89**(38): p. 418-428.

2. Reid, A.E., M.K. Hendricks, P. Groenewald, et al., *Where do children die and what are the causes? Under-5 deaths in the Metro West geographical service area of the Western Cape, South Africa, 2011.* S Afr Med J, 2016. **106**(4): p. 51.

3. Vidyasagar, D., *"Half a Century of Evolution of Neonatology: A Witness's Story".* The Indian Journal of Pediatrics, 2015. **82**(12): p. 1117-1125.

4. Shah, P.S., *Neonatal Intensive Care - The Only Constant Is Change.* N Engl J Med, 2017. **376**(7): p. 694-696.

5. Tseng, Y.H., C.W. Chen, H.L. Huang, et al., *Incidence of and predictors for short-term readmission among preterm low-birthweight infants.* Pediatr Int, 2010. **52**(5): p. 711-717.

6. Slimings, C., K. Einarsdottir, R. Srinivasjois, et al., *Hospital admissions and gestational age at birth: 18 years of follow up in Western Australia.* Paediatr Perinat Epidemiol, 2014. **28**(6): p. 536-544.

7. Mourani, P.M., J.P. Kinsella, G. Clermont, et al., *Intensive care unit readmission during childhood after preterm birth with respiratory failure.* J Pediatr, 2014. **164**(4): p. 749-755 e3.

8. Elder, D.E., R. Hagan, S.F. Evans, et al., *Hospital admissions in the first year of life in very preterm infants.* J Paediatr Child Health, 1999. **35**(2): p. 145-150.

9. Smith, V.C., J.A. Zupancic, M.C. McCormick, et al., *Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia.* J Pediatr, 2004. **144**(6): p. 799-803.

10. Escobar, G.J., S. Joffe, M.N. Gardner, et al., *Rehospitalization in the first two weeks after discharge from the neonatal intensive care unit.* Pediatrics, 1999. **104**(1): p. e2.

11. Ralser, E., W. Mueller, C. Haberland, et al., *Rehospitalization in the first 2 years of life in children born preterm.* Acta Paediatr, 2012. **101**(1): p. e1-5.

12. Hong, T., S. Bolisetty, B. Bajuk, et al., *A population study of respiratory rehospitalisation in very preterm infants in the first 3 years of life.* J Paediatr Child Health, 2016. **52**(7): p. 715-721.

13. Brissaud, O., F. Babre, L. Pedespan, et al., *Rehospitalization of very preterm infants in the first year of life. Comparison of 2 groups: 1997 and 2002.* Arch Pediatr, 2005. **12**(10): p. 1462-1470.

14. Underwood, M.A., B. Danielsen, and W.M. Gilbert, *Cost, causes and rates of rehospitalization of preterm infants.* J Perinatol, 2007. **27**(10): p. 614-619.

15. Kuint, J., L. Lerner-Geva, G. Chodick, et al., *Rehospitalization Through Childhood and Adolescence: Association with Neonatal Morbidities in Infants of Very Low Birth Weight.* J Pediatr, 2017. **188**: p. 135-141 e2.

16. Taylor, J.B., M.A. Go, M.F. Nyp, et al., *Rehospitalization in Infants Born < 29 Weeks' Gestation during the First 2 Years of Life: Risk Assessment.* Am J Perinatol, 2016. **33**(1): p. 24-33.

17. Gunville, C.F., M.K. Sontag, K.A. Stratton, et al., *The scope and impact of early and late preterm infants admitted to the PICU with respiratory illness.* J Pediatr, 2010. **157**(2): p. 209-214 e1.

18. Mukhopadhyay, K., D. Louis, G. Mahajan, et al., *Longitudinal growth and post-discharge mortality and morbidity among extremely low birth weight neonates.* Indian Pediatr, 2014. **51**(9): p. 723-726.

19. Blencowe, H., S. Cousens, D. Chou, et al., *Born Too Soon: The global epidemiology of 15 million preterm births.* Reproductive Health, 2013. **10**(Suppl 1): p. S2-S2.

20. Slater, A., F. Shann, and G. Pearson, *PIM2: a revised version of the Paediatric Index of Mortality.* Intensive Care Med, 2003. **29**(2): p. 278-85.

21. Solomon, L.J., B.M. Morrow, and A.C. Argent, *Paediatric Index of Mortality scores: An evaluation of function in the paediatric intensive care unit of the Red Cross War Memorial Children's Hospital.* Southern African Journal of Critical Care (Online), 2014. **30**: p. 9-13.

22. Ambalavanan, N., W.A. Carlo, S.A. McDonald, et al., *Identification of extremely premature infants at high risk of rehospitalization.* Pediatrics, 2011. **128**(5): p. e1216-1225.

23. Mills, R.J. and M.W. Davies, *Enteral iron supplementation in preterm and low birth weight infants.* Cochrane Database of Systematic Reviews, 2012(3).

24. Escobar, G.J., M.C. McCormick, J.A. Zupancic, et al., *Unstudied infants: outcomes of moderately premature infants in the neonatal intensive care unit.* Arch Dis Child Fetal Neonatal Ed, 2006. **91**(4): p. F238-244.

25. Lee, J.H., Y.S. Chang, C. Committee on Data, et al., *Use of Medical Resources by Preterm Infants Born at Less than 33 Weeks' Gestation Following Discharge from the Neonatal Intensive Care Unit in Korea.* J Korean Med Sci, 2015. **30 Suppl 1**: p. S95-S103.

26. Zar, H.J., S.A. Madhi, D.A. White, et al., *Acute viral bronchiolitis in South Africa: Strategies for management and prevention*. 2016. Vol. 106. 2016.

8. Appendices

Appendix 1: The Study Protocol

A Description of Premature and Ex-Premature Infants Admitted to the Paediatric Intensive Care Unit in the First Six Months of Life

Student: Grace Thangam Mathew

MTHGRA005

Research Protocol

Submitted as part of the fulfilment of requirements for the degree

Master of Medicine (MMed) Paediatrics

University of Cape Town
Faculty of Health Sciences
Supervisor: Dr Beyra Rossouw
Department of Paediatric Critical Care, Red Cross War Memorial Children's Hospital

A Description of Premature and Ex-Premature Infants Admitted to a Paediatric Intensive Care Unit in the First Six Months of Life

Care of the premature newborn is an ever-evolving medical field. There have been dramatic advancements in the knowledge and interventions related to care of any premature infant. Survival is not only a possibility, but most often the expectation, in many situations once considered to be futile. However, the risk in these cases is that a premature infant may survive with significant morbidity and demands on the health care system and family in the future.

There is very little data available worldwide regarding premature infants that require readmission to a neonatal or paediatric intensive care unit (PICU). The intention of this study is to look specifically at unplanned admissions of preterm infants to PICU at Red Cross War Memorial Children's Hospital (RXH). The purpose is two-fold. Firstly, describing the incidence and course of these admissions and secondly, to identify risk factors in preterm infants that increase the likelihood of a long stay in PICU or mortality. Our hope is that data from this study may be used to identify infants who are at increased risk of serious illness or death after discharge from a neonatal unit. Unfortunately, this study will not include infants who demise at home or prior to admission into this unit. As a result, there is potential to underestimate the risk of morbidity and mortality in premature infants.

In addition to this, we will compare the mortality rate as well as the length of stay of premature infants to all children admitted to the PICU in the same time period. We will also briefly report what percentage of the admissions to the PICU are premature infants within this time period.

This is valuable information as it addresses the impact of preterm births within the health care system in Cape Town, South Africa. It may also provide insight into the outcome of preterm infants and flag any factors that potentially increase the likelihood of severe illness after discharge from a neonatal unit. This data would be used to improve protocols and long-term care plans for premature babies.

Definitions

As per the World Health Organisation (1), the classification of premature and underweight infants is as follows:

- <28 weeks: extremely preterm
- 28 to <32 weeks: very preterm
- 32 to <37 weeks: moderate to late preterm
- <1000g: extremely low birth weight (ELBW)
- 1000g to <1500g: very low birth weight (VLBW)
- 1500g to <2500g: low birth weight (LBW)

Gestational age (GA) of any infant is determined using one of three options which include antenatal ultrasonography, calculations based on last menstrual period and scoring based on physical examination of the neonate, such as the Ballard Score. An early ultrasound done up to 23 completed weeks is considered to be the most accurate estimate of GA. Soon after birth, GA of a child is determined by the attending clinician based on one or more of the above-mentioned assessments and is often inaccurate.

The following scores are used worldwide and will be used as indicators in this study:

- The Paediatric Index of Mortality (PIM) is a score that was designed to estimate mortality risk during an admission to a PICU (2). The score uses data from the time of admission and is validated for monitoring of quality of care provided by a PICU. The score was revised in 2003 and is now referred to as PIM2.
- The Paediatric Risk of Mortality Score (PRISM) is designed for use in any PICU and uses various physiologic variables to assist with mortality risk assessment (3).

Literature review

Currently, in Cape Town West Metro, there is no data regarding outcome of patients discharged from the neonatal units. A search of the literature revealed some interesting research that I will explore further.

Readmission Diagnoses

The reasons for hospital readmissions in premature infants have been quite extensively researched. Several common diagnoses have been identified in various studies, as discussed below. Kuzniewicz et al. published a literature review focused on readmissions and emergency department visits in moderate preterm, late preterm and term infants in the first thirty days post discharge (4). The studies reviewed were all performed in the United States of America, Canada and the United Kingdom. They found that the commonest cause for readmission was for jaundice and feeding problems in the late pre-term, early term and term patients. But after excluding these admissions, in all the subgroups, the most common reason for readmission was found to be presumed sepsis.

A retrospective study on infants that required readmission in the first two weeks after discharge from a neonatal unit (NU) in various centers in the USA showed similar results (5). They found, once again, that feeding difficulty and jaundice were the most common reasons for readmission in infants with a gestational age above 33 weeks. A study of the outcomes of infants born before 28 weeks GA in several centers in Quebec, Canada (6) found that readmission was most commonly due to a respiratory illness. Other reasons for readmission included surgery, gastro-intestinal/nutrition problems, other infections and neurological problems. These children were followed up to a corrected age of 18 months.

PICU readmission of premature babies

Admission to any intensive care unit (ICU) carries significant morbidity and mortality risks. Research regarding readmissions of premature babies specifically to PICU is limited. A study done in Denver, Colorado by Cameron et al (7) in 2010 looked at all children below the age of 2 years that required admission to a PICU. They found that preterm infants were at an increased risk of admission secondary to respiratory illness in their centers. Notably, preterm infants required longer PICU and hospital stay, and utilised more resources than term infants.

Mourani et al (8) found that nearly 1 in 5 premature babies required readmission to an ICU after

discharge from a neonatal intensive care unit (NICU) over the next 4.5 years.

A study done in India found an 11% mortality rate and a 44% readmission rate in a group of extremely low birth weight infants who were followed up for a period of 2 years (9). Although this study was not looking specifically at readmissions to ICU, these results are alarming.

Unfortunately, there is limited data regarding readmissions of premature infants to ICU, but there are some identifiable risk factors for readmission of these children over the next few years of their lives. Kuzniewicz et al (4) found that the population at highest risk of readmission was the moderate preterm infants. Some identifiable risk factors for readmission in their study group included preterm infants and those with a length of stay over 5 days in a neonatal unit. But other evidence seems to be more ambivalent regarding a relationship with length of stay and risk of readmission (10). Moderate preterm infants are twice as likely to be readmitted when compared to term infants up to the age of 5, especially with exposure to passive smoking, early respiratory infections, and those with a family history of asthma (11). On the other hand, late-preterm infants are also at increased risk of readmission and mortality (12).

There is also some evidence to indicate that those born by caesarean section have a decreased risk of readmission (13). Infants who required mechanical ventilation are at increased risk of readmission to hospital (14)- in particular, males, those with increased duration of neonatal admission, or prolonged oxygen therapy, and those with severe intracranial haemorrhage.

A review done in Australia by Doyle et al (15) in 2002 looked specifically at infants with extremely low birth weight (ELBW) below 1000 g in studies done from 1980 to 1997. They found that most of the studies reported readmission rates close to or above 50%, although severity of the illness wasn't mentioned. This increased risk persisted into later childhood as well. Infants with bronchopulmonary dysplasia (BPD) were also found to have higher rates of readmission and more likely to require multiple readmissions. Some other identifiable risk factors included male gender, smoking in pregnancy and chronic lung disease (16). In infants born before 28 weeks GA, the likelihood of readmission was increased in socially disadvantaged groups. There was no identifiable increase in risk related to birth weight or GA. Respiratory infection was the commonest diagnosis in patients requiring rehospitalisation. Luu et al (6) also found a 46% readmission rate in infants born below 28 weeks GA. Infants with BPD, particularly those on home oxygen, and those with severe brain injury, prolonged neonatal stay and using an apnoea monitor at home were at increased risk of readmission when they were followed up until 18 months corrected age. The development of BPD has a significant morbidity throughout childhood (17, 18). Some other identifiable risk factors include shunt surgery for hydrocephalus, necrotising enterocolitis (stage II or worse) and spontaneous perforation of the gastrointestinal tract (17).

In summary, it seems that ELBW and extremely premature infants tend to be at increased risk of readmission (up to 50%). Several studies identified chronic lung disease/BPD as a common characteristic in infants requiring readmission. This seems consistent even with follow-up into the second year of life. There is some discrepancy in data related to the impact of length of stay in the neonatal unit.

Another important consideration in the care of preterm infants is discharge criteria. These criteria need to balance the safety of the infant with the cost of medical care. Both Seki et al (19) and Picone et al (20) indicates that there is a safe approach to early discharge of premature infants, particularly in a first world setting. Unfortunately, there is very limited research comparing discharge criteria and risk of readmission. There is some risk identified with a length of stay less than two days with an increased likelihood of missed comorbidities and complications in all admissions (21).

Seki et al (19) studied the 3 month and 1 year readmission rates of preterm infants (22 to 34 weeks GA) in a NICU in Japan. These infants were discharged regardless of age or weight if they were clinically well, free of apnoeas and bradycardia for a week, gaining weight with lactation and with good temperature regulation and home environments. They found that 9.5% of their infants in total, but 26.9% of those with GA less than 26 weeks, required readmission. Considering the low rate of readmission, their criteria for discharge were considered appropriate.

Picone et al (20) found that in their center it was appropriate to discharge clinically well infants at a mean weight close to 1900g if the infant was born under 32 weeks GA and/or a birth weight lower than 1500g. Only 8 of the 122 infants included in the study required readmission within 33 days post discharge. These patients were not followed up beyond this period.

Summary

Although limited data is available, readmissions rates are consistently higher in premature infants, some up to 50%. There seem to be risk factors that increase the likelihood of readmission. These include early preterm infants, BPD and those requiring mechanical ventilation in NICU. One of the above studies also found that socio-economic circumstance of the family may play a part as well. Length of stay in a NU seems to have an influence, although this seems to vary with gestational age. Identifying appropriate and safe discharge criteria may decrease the likelihood of readmission. Respiratory illness and presumed sepsis seem to be the most common diagnoses in infants requiring readmission. Feeding difficulty and jaundice are more common readmission diagnoses in late preterm infants. Unfortunately, it is difficult to extrapolate these results to a South African setting. Health resource limitations may influence early neonatal discharge; and family socio-economic circumstances may impact readmission rates.

Purpose of the Study

i. To describe the unplanned admissions of premature or ex-premature babies to RXH PICU within the first six months of life.

ii. To identify risk factors associated with prolonged PICU admission and/or mortality of premature or ex-premature infants admitted to RXH PICU.

Methodology

Study Design

A longitudinal observational study of all babies admitted to RXH PICU with the history of premature birth. Only babies with a chronological age of six months or less on PICU admission will be included. Data will be collected prospectively in a period from March 2016 to October 2016.

Setting

Within the Cape Town West Metro service, Mowbray Maternity Hospital (MMH), New Somerset Hospital (NSH) and Groote Schuur Hospital (GSH) bear the brunt of secondary and tertiary care of neonates. Unwell newborns are admitted directly into the neonatal unit. Once they are determined to be safe for discharge, they are referred to the Maternity-Obstetric Units (MOUs) in local community health centers if they are considered to be low-risk infants. High-risk infants are followed up at MMH, where specialists are on hand to deal with any major concerns.

If these infants require readmission for any reason, they are generally admitted to the nearest paediatric unit. In the Cape Town West Metro district, within the state health sector, the only paediatric intensive care unit is within the Red Cross War Memorial Children's Hospital. RXH is a South African tertiary academic children's hospital which has a multidisciplinary, 22 bed medical and surgical PICU where the study will be performed. There are approximately 400 ex-premature infants admitted to this unit every year.

Enrolment of patients

Patients will be enrolled by the student researcher who will review admissions in the PICU at least five days a week and collect data as detailed below. We anticipate that there will be up to 200 patients enrolled in this study.

Inclusion criteria

- All babies admitted to RXH PICU
    - with the history of being born premature at GA of <37 weeks at birth
    - and have been discharged from a neonatal unit
    - and have a chronological age of six months or less on RXH PICU admission

Exclusion criteria

- All premature babies admitted to RXH PICU directly from a neonatal unit for ongoing specialized tertiary care before being discharge from the NICU.

Interventions

Routine PICU care will be provided to all patients during their PICU stay. No study intervention will be done besides routine care.

Data collection

Data will be collected prospectively from patient folders, PICU database, discharge summaries and Road to Health booklets. The Road to Health Booklet (RTHB) is a tool to record information relating to growth and development of a child. Some useful information it provides includes birth and perinatal history, immunisation status, growth charts and a record of outpatient and inpatient visits.

PICU data will include:

- Reason for PICU admission e.g. apnoea/shock/respiratory failure/dehydration
- PICU discharge diagnosis
- Length of stay in PICU
- Interventions in PICU: e.g., ventilation, inotropes
- PIM2 and PRISM score in PICU admission
- Admission age, weight, haemoglobin
- Outcome: Survival to PICU discharge, length of stay, length of ventilation days
- Previous admissions to PICU

We will collect data on birth history and NU care to identify risk factors for PICU readmission. Neonatal records of patients from GSH or MMH should be available, but there may be difficulties accessing records of patients from other institutions.

Neonatal and general data will include:

- Gender
- GA and birth weight
- Neonatal admission: length of stay, discharge weight,
- Feeding choice
- Congenital abnormalities or syndrome
- Mode of delivery
- HIV status: exposure and infection
- Immunisation Status

The available information will be collected using the data capture sheet attached and stored on a Microsoft Excel spreadsheet. A study number linked to the allocated hospital number will be used to identify patients, thereby maintaining patient confidentiality. The hospital number will be used to identify multiple readmissions of the same patient to avoid duplication of the same patient, but all admissions will be recorded.

Data Analysis

Statistical analysis will be performed by Professor Brenda Morrow. Data will be tested for normality using Shapiro Wilks W test, and descriptive statistics presented as appropriate for distribution. Univariate analysis will be conducted to assess associations between collected data and binary outcome measures, using t tests, Mann Whitney U tests and chi-square tests according to normality and type of data. Variables found to be associated with the outcome of mortality on univariate analysis will be entered into a stepwise logistic regression model to determine independent risk factors. Correlation coefficients between continuous variables and length of ICU stay will be analysed using Spearman R or Pearson Product Moment tests according to distribution. Statistical significance will be defined as $p < 0.05$.

Risks and Benefits

This is a descriptive study and patients will not be exposed to any interventions, nor will patient management be affected by the information collected during the study. As such, there is no specific physical risk or benefit to any of the patients included in the study. The following measures will be in place to protect patient confidentiality and anonymity. Patient names will not be collected, instead patients will be allocated unique study numbers linked to the hospital folder number and related to chronological entry into the study. This number will be separate from the hospital or ICU admission number. The link to both numbers will be stored in password protected documents. All of the data will be stored on a database on a private computer. The data and statistics will only be accessible to the principal investigators.

In the long term, it is hoped that identifying any factors that increase risk of severe illness may lead to more appropriate follow-up and monitoring of premature infants.

The principle of autonomy cannot be applied to these young infants, but this is the most vulnerable and, as such, valuable time to assess this group of patients. For the information relevant to this study, it is difficult to extrapolate data from older children or adults. Therefore, it is necessary to include this group of patients.

Informed Consent

As this is a descriptive study, there is no alteration to treatment for patients included in the study. Information will be collected only from patient folders, the PICU database, discharge summaries and Road to Health booklets. There will not be an interview with the parents or legal guardians of the patients.

Informed consent will be taken from the parents or legal guardian of the patient. A hospital translator or a PICU staff member will be available to assist with translation if required.

Cost

Children will receive standard PICU and hospital care. There will be no additional laboratory or hospital expenses.

Ethical considerations

Full approval will be obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town and Red Cross War Memorial Children's Hospital.

We understand that the privacy of these infants and their families is of the utmost importance. As detailed above, every effort will be made to maintain patient confidentiality. All research will adhere to the requirements stated in the Declaration of Helsinki, 2013.

Outcome

Data will be presented at a National Paediatric conference and will be published in a peer reviewed journal.

Limitations

The data for the study will be collected from patient folders, discharge summaries and RTHBs. The information available will be heavily reliant on thorough note-keeping from both the PICU and the neonatal units. As a result, the data collected may be incomplete and affect the final analysis of available information related to PICU admission.

Infants from MMH, NSH and GSH neonatal units should have adequate data, but the information from other units may not be easily available. This will affect the interpretation of data from the admission to the neonatal unit.

As we are not collecting data on infants who demise at home or prior to admission to PICU at RXH, the data may underestimate the actual morbidity and mortality of premature infants after discharge from a neonatal unit.

Children will be recruited into this study based on their GA. As discussed earlier, GA is determined using information from antenatal ultrasounds, or last menstrual period of the mother or a score based on physical examination. These estimates are often inaccurate as the above criteria are fairly unreliable and rely heavily on clinician skill or the mother's memory.

The aim of this study is to describe the incidence and course of unplanned readmissions, within the first six months of life, of infants born preterm to the paediatric intensive care unit at Red Cross War Memorial Children's Hospital. It may provide insight into the impact of premature infants on the health care system, as well as the outcome of these infants. In addition, the study may identify risk factors that increase the likelihood of a long stay in PICU or mortality. The data collected has the potential to improve current protocols and long-term care of premature babies.

Bibliography

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born Too Soon: The global epidemiology of 15 million preterm births. Reproductive Health. 2013;10(Suppl 1):S2-S.

2. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. Intensive care medicine. 2003;29(2):278-85.

3. Bhadoria P, Bhagwat AG. Severity scoring systems in paediatric intensive care units. Indian J Anaesth. 2008;52(suppl 5):663-75.

4. Kuzniewicz MW, Parker SJ, Schnake-Mahl A, Escobar GJ. Hospital readmissions and emergency department visits in moderate preterm, late preterm, and early term infants. Clin Perinatol. 2013;40(4):753-75.

5. Escobar GJ, Joffe S, Gardner MN, Armstrong MA, Folck BF, Carpenter DM. Rehospitalization in the first two weeks after discharge from the neonatal intensive care unit. Pediatrics. 1999;104(1):e2.

6. Luu TM, Lefebvre F, Riley P, Infante-Rivard C. Continuing utilisation of specialised health services in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed. 2010;95(5):F320-5.

7. Gunville CF, Sontag MK, Stratton KA, Ranade DJ, Abman SH, Mourani PM. Scope and impact of early and late preterm infants admitted to the PICU with respiratory illness. J Pediatr. 2010;157(2):209-14 e1.

8. Mourani PM, Kinsella JP, Clermont G, Kong L, Perkins AM, Weissfeld L, et al. Intensive care unit readmission during childhood after preterm birth with respiratory failure. J Pediatr. 2014;164(4):749-55 e3.

9. Mukhopadhyay K, Louis D, Mahajan G, Mahajan R. Longitudinal growth and post-discharge mortality and morbidity among extremely low birth weight neonates. Indian pediatrics. 2014;51(9):723-6.

10. Goyal N, Zubizarreta JR, Small DS, Lorch SA. Length of stay and readmission among late preterm infants: an instrumental variable approach. Hospital pediatrics. 2013;3(1):7-15.

11. Vrijlandt EJ, Kerstjens JM, Duiverman EJ, Bos AF, Reijneveld SA. Moderately preterm children have more respiratory problems during their first 5 years of life than children born full term. American journal of respiratory and critical care medicine. 2013;187(11):1234-40.

12. Tsai ML, Lien R, Chiang MC, Hsu JF, Fu RH, Chu SM, et al. Prevalence and morbidity of late preterm infants: current status in a medical center of Northern Taiwan. Pediatrics and neonatology. 2012;53(3):171-7.

13. Moyer LB, Goyal NK, Meinzen-Derr J, Ward LP, Rust CL, Wexelblatt SL, et al. Factors associated with readmission in late-preterm infants: a matched case-control study. Hospital pediatrics.

2014;4(5):298-304.

14. Mourani PM, Kinsella JP, Clermont G, Kong L, Perkins AM, Weissfeld L, et al. Intensive care unit readmission during childhood after preterm birth with respiratory failure. J Pediatr. 2014;164(4):749-55.e3.

15. Doyle LW, Ford G, Davis N. Health and hospitalisations after discharge in extremely low birth weight infants. Seminars in Neonatology. 2003;8(2):137-45.

16. Ralser E, Mueller W, Haberland C, Fink FM, Gutenberger KH, Strobl R, et al. Rehospitalization in the first 2 years of life in children born preterm. Acta Paediatr. 2012;101(1):e1-5.

17. Ambalavanan N, Carlo WA, McDonald SA, Yao Q, Das A, Higgins RD. Identification of extremely premature infants at high risk of rehospitalization. Pediatrics. 2011;128(5):e1216-25.

18. Greenough A. Long-term respiratory consequences of premature birth at less than 32 weeks of gestation. Early human development. 2013;89 Suppl 2:S25-7.

19. Seki K, Iwasaki S, An H, Horiguchi H, Mori M, Nishimaki S, et al. Early discharge from a neonatal intensive care unit and rates of readmission. Pediatr Int. 2011;53(1):7-12.

20. Picone S, Paolillo P, Franco F, Di Lallo D. The appropriateness of early discharge of very low birth weight newborns. J Matern Fetal Neonatal Med. 2011;24 Suppl 1:138-43.

21. Lee EW. Selecting the best prediction model for readmission. Journal of preventive medicine and public health = Yebang Uihakhoe chi. 2012;45(4):259-66.

Appendix 2: HREC Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 March 2016

HREC REF: 103/2016

Dr B Rossouw
Intensive Care Unit
Red Cross War Memorial Children's Hospital

Dear Dr Rossouw

PROJECT TITLE: A DESCRIPTION OF PREMATURE AND EX-PREMATURE INFANTS ADMITTED TO A PAEDIATRIC INTENSIVE CARE UNIT IN THE FIRST SIX MONTHS OF LIFE- (Masters candidate- Dr Grace Mathew).

Thank you for submitting response letter to the Faculty of Health Sciences Human Research Ethics Committee dated 04th March 2016.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until 30 March 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, Dr Grace Mathew will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

pp T Burgers

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.6.2019
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	1/6/18

Comments to PI from the HREC
All data collection completed by October 2018. Currently in process of completing data analysis.

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	31/05/2018		
HREC REF Number	103/2018	Current Ethics Approval was granted until	March 2017
Protocol title	A Description of Premature and Ex-Premature Infants Admitted to the Paediatric Intensive Care Unit in the First Six Months of Life		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes	☑ No	
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	Not applicable		
Principal Investigator	Dr Beyra Roesouw		
Department / Office Internal Mail Address	Beyra.roesouw@uct.ac.za		

Additional number of participants still required	N/A

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	None

6. Cumulative summary of participants

Total number of participants who provided consent	29
Number of participants determined to be ineligible (i.e. after screening)	None
Number of participants currently active on the study	None
Number of participants completed study (without events leading to withdrawal)	29
Number of participants withdrawn at participants' request (i.e. changed their mind)	None
Number of participants withdrawn by PI due to toxicity or adverse events	N/A
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	N/A
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	N/A
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	N/A

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
Data collection completed in October 2016 and currently completing data analysis and preparing for submission of mini-dissertation.

8. Protocol violations and exceptions (tick ✓ all that apply)

☑	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☑ No
If yes, please explain:	

12. Level of risk (tick ✓)

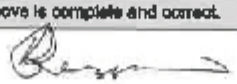
12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☐	Shown no change
If there has been a change, please explain:	
Not applicable	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
Not applicable

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☑ No
If yes, please explain and if necessary attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHSC13):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	31/5/2018

Appendix 3: Data collection form

PICU Admission

Discharge Diagnosis (A)					
Respiratory	Pneumonia	Bronchiolitis	Upper Airway	Aspiration	Asthma
GIT	Bowel Obstruction		Gastroenteritis	NEC	
CVS	Congenital Heart Disease		Myocarditis		
Neurological	Seizures	Meningitis	Hydrocephalus	Other	
Bacterial sepsis	Group B Strep	Nosocomial	Other		
Viral	Adenovirus	RSV	Other		
Vaccine-	Yes	No	Diag:		
Non-medical	Trauma	Elective Surgery	Other		
Other					

Reason for admission (B)				
CVS	Cardiac Failure	Cardiogenic Shock	Cyanotic Spells	
Respiratory	Respiratory failing needing intubation and ventilation		Requiring CPAP	
Neurological	Seizures		Decreased level of consciousness	
Shock	Septic Shock	Hypovolaemic shock	Cardiogenic Shock	Other
Other	Electrolyte	Apparent life threatening event		Apnoea
Non-medical	Trauma		Elective Surgery	
Other				

PICU admission (C)					
Outcome	Demised in PICU		Discharged from PICU		
Length of stay in PICU	>7 days	4-7 days	2-3 days	1 day	<1 day
Resp support	IPPV	CPAP/NPO2	Room Air		
Ventilation Days	>7 days	4-7 days	2-3 days	1 day	<1 day
CVS support	Inotropes		No inotropes		
Anaemia	Transfused	Anaemia	Not anaemic		
Other interventions	Dialysis	Surgery	Other		
PIMS Score					
Previous PICU					
Other					

Patient characteristics and Neonatal Unit (NU) Admission (D)					
Gender	Male		Female		
Gestational Age					
Mode of delivery	NVD: Inborn or Outborn		Caesarean Section		
Actual age at	<1 month	1-2 months	2-4 months	4-6 months	
Corrected age	35-<37weeks	37->40 weeks	40 wks to <1 month	1-<3 months	>/= 3 month
Weight at	<2 kg	2-<4 kg	4-<6 kg	>6 kg	
Birth weight					
Current weight	Weight below -2 Z score		Weight above -2 Z score		
Trend since NU	Falling off z-score trend		Following trend z-score		
Length of stay in	<4 days	4-<7 days	1-2 weeks	2-4 weeks	>4 weeks
NU: D/C wt					
Time since discharge from neonatal unit	<1 week	1-2 weeks	> 2 weeks to 1 month	>1 month	> 2 months
Feeding at readmission	Breast	Formula	Mixed	Non-milk feeds/water introduced	
Immunisation	UTD	Not UTD	Delayed, if yes, how long?	Not documented	
HIV Status	Negative	Exposed, -ve	Infected, HAART	Infected, no HAART	
Other					

Morbidities identified in the Neonatal Unit (E)						
Respiratory	Intubation and ventilation >72 hours	Chronic lung disease (required oxygen at 36w corrected age)	On home oxygen			
Congenital abnormality	Cardiac lesions	Syndromic	Other			
Pre-discharge cranial US	Normal	Periventricular leucomalacia	Gr 3 - 4 IVH	Other abnormality		
Complications	Moderate to severe HIE	Severe NNJ above exchange value	Sepsis	NEC	Cardiac surgery	Other surgery
Other	Late infection	Retinopathy of prematurity				

Appendix 4: Instructions to authors of chosen journal

South African Journal of Child Health

The *South African Journal of Child Health* is an online, quarterly, peer reviewed medical journal covering all aspects of child health.

Author Guidelines

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

To submit a manuscript, please proceed to the *SAJCH* Editorial Manager website: Editorial Manager

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees,

gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAJCH* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAJCH.*

Copyright notice

The Agreement form should be uploaded along with other submissions files and any submission will be considered incomplete without it *[forthcoming].*

Material submitted for publication in the *SAJCH* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAJCH* does not hold itself responsible for statements made by the authors. The corresponding author should also indicate if the research forms part of a postgraduate short report, dissertation or thesis.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAJCH* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to any third party without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAJCH* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note thatit is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAJCH is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAJCH* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Editorials, Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

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

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- 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)'.
- 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.

SAJCH is a Journal on child health, therefore for articles involving 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 Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

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. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. 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.

- May include up to 6 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, 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. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

***Scientific letters*/short reports**

These include case reports, side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Review articlesshould always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a precis of reviews published in the international literature

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important

- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJCH or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of 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 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.) consecutively as they are referred to 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.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

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Do not: use separate columns for *n* and %:

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- 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.
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  - 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.

NOTE: no . after the v

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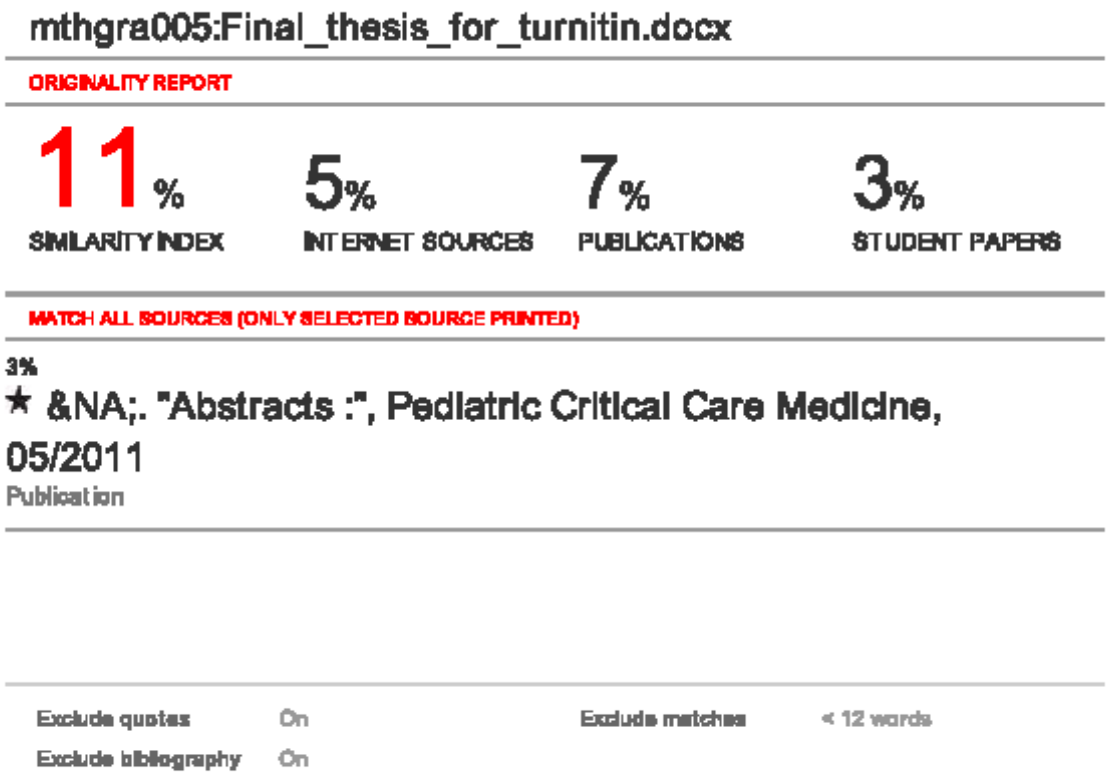

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