A STUDY TO DETERMINE THE CAUSES OF DEATH IN NEONATES WEIGHING <1500g AT KLEKSDORP HOSPITAL

A research report submitted to the Faculty of Medicine, University of the Witwatersrand in fulfilment of the requirements for the degree of Master of Medicine (MMed) in the discipline of Paediatrics

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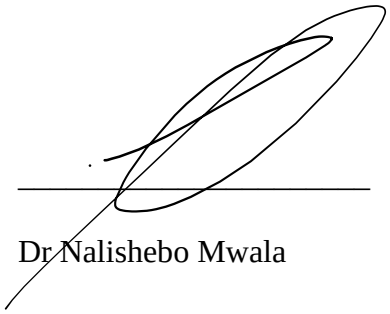
Declaration

I, Nalishebo Mwala, declare that this research submission is my own, unaided work. It has been submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other university.



Dr Nalishebo Mwala

1 February 2023, Johannesburg

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Dedication

This is dedicated to my parents, Dr Philip F Mwala and Mrs Deborah M Mwala

Acknowledgements

Thank you to the doctors and nurses committed to the care of neonates

Thank you to the Clinical manager at Klerksdorp Hospital for giving permission to conduct this study

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NM

Definitions

Anaemia	haemoglobin usually <10g/dL or level at which the patient becomes symptomatic requiring a blood transfusion
Asphyxia	decreased perinatal oxygen intake resulting in hypoxia and metabolic acidosis
Early neonatal death	death occurring between 0 and 7 days of life
Extremely low birthweight	neonates with a birthweight of <1000g
Hyperglycaemia	an HGT >11.1 mmol/L
Hypoglycaemia	an HGT < 2.6 mmol/L
Hypotension	a low blood pressure at which perfusion is compromised and inotropes are required
Late neonatal death	death occurring between 7 and 28 days of life
Metabolic acidosis	a pH <7.25, HCO3 mmol/L <15 and BE <-5 mmol/L
Patent ductus arteriosus	based on clinical suspicion with a wide pulse pressure and a cardiac murmur (Echo confirmation not always possible)
Pulmonary haemorrhage	acute bleeding from the lung/respiratory tract usually noted as fresh blood in the endotracheal tube resulting in haemodynamic instability and respiratory failure
Renal dysfunction	a rise in creatinine levels using AKIN criteria
Sepsis	for the purposes of this study this was defined as a positive blood culture or suspected infection based on history and/or clinical suspicion and/or biochemical markers
Very low birthweight	neonates with a birthweight of <1 500g

Submissible paper to SAJCH

A study to determine the causes of death in neonates weighing <1500g at Klerksdorp Hospital

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Background

The continuing challenge of neonatal mortality in very low birth weight (VLBW) neonates in South African hospitals highlights the need to better understand the causes of these deaths as well as their associated modifiable factors.

Objectives

1. Determine the causes of death and factors that contribute to death in VLBW neonates at Klerksdorp Hospital (KH)
2. Determine key modifiable factors to improve the survival of VLBW neonates at KH.

Methods

Retrospective, descriptive study based on the review of 183 patient records (100 who survived and 83 who died) between January 2015 to December 2016. The study population is from the neonatal unit at a secondary hospital in the North-west province of South Africa. The unit consists of eight beds with ventilatory support. Fifty-five Perinatal Problem Identification Program (PPIP) forms were audited to determine causes of death and associated modifiable factors. Logistic regression analysis was used to determine predictors of death.

Results

The most common causes of death were 1) sepsis (24%), 2) extreme multiorgan immaturity (20%) and with the most vulnerable neonates born between 26 and 32weeks' gestation. An increase in birthweight is shown to incur protection against death (OR 0.993, CI 0.989-0.996, p = 0.000). Key predictors of death are metabolic acidosis during the course of their NICU admission (OR 17.785, CI 4.711-67.145, p = 0.000) and hypotension-requiring-inotropes (OR 26.074, CI 5.403-125.827, p = 0.000) secondary to septic shock. Critical modifiable factors include preventing nosocomial sepsis (18%), timely initiation of antenatal care (12%) and improving timeous health seeking behaviour (10%), administration of antenatal steroids (6%) and availability of adequately trained medical personnel (6%).

Conclusion

Sepsis is the leading cause of death in very low birth weight neonates. Its complications in the form of metabolic acidosis and septic shock requiring inotropic support are key predictors of death. Seventy seven percent the deaths occurred in the first week of life, highlighting a vital window for intervention. Key modifiable factors pertain to medical and patient factors. Barriers that may preclude this lie in the poor socio-economic setting of the population that is mostly peri urban with constrained resources.

Introduction

In 2014, reflecting on persistently high neonatal mortality rates (NMRs), the World Health Organisation (WHO) and United Nations Children's Fund (UNICEF) developed a roadmap for ending preventable new-born deaths through the articulation of the 'Every New-born' Action Plan (ENAP). [1,2,3], The plan seeks to reduce the global NMR to 7/1000 live births by 2035 as compared to the sustainable development goal (SDG) target of 12/1000 live births by 2030 [1,2,3] To achieve this, several healthcare pillars are addressed which include empowering communities, forming partnerships, increasing healthcare coverage, and improving the quality of health care delivery. [3]

South Africa has made improvements over the past three decades with a reduction in NMR of 21/1000 to 11/1 000 as of 2020. This is within the third SDG and a significant stride towards the ENAP target [3,4,5] It has been shown that the advent of various medical interventions as routine such as antenatal steroids and early surfactant with nasal continuous positive airway pressure (NCPAP) can account for this improvement. [6,7,8] To continue the forward momentum, this study has specifically earmarked very low birthweight (VLBW) neonates for review. Given the disproportionate number of deaths they account for, and the limited progress in the rest of sub-Saharan Africa, there are still strides to be made in reducing VLBW mortality. [5,6,9]

Changes in interventions/protocols through reviewing outcomes can significantly improve the survival rates of neonates.[8] This study aims to understand what factors/ complications amongst VLBW neonates increase their risk of death and understand the associated modifiable factors. The information generated from this study is expected to add to current knowledge, reinforce the need for ongoing clinical audits and establish good clinical practice and counselling services, particularly in secondary hospitals with limited resources.[7]

Methods

Study design

This is a retrospective, descriptive study conducted at Klerksdorp Hospital (KH) in The North-West province of South Africa. It is an academic hospital affiliated with the University of the Witwatersrand (WITS). It is classified as a secondary level hospital, although it offers some tertiary level services.

Hospital facilities

The Neonatal Unit consists of 40 beds of which eight are neonatal intensive care beds (NICU), nine are high care, and 23 are low care. NICU provides respiratory support in the form of mechanical ventilation and continuous positive airway pressure (CPAP) as well as inotropic support. The weight cut-off for mechanical ventilation is 900g and there is no CPAP cut-off. High care is allocated for sick babies who do not require ventilator or inotropic support.

Patients admitted to KH are mainly from within the Kenneth Kaunda district of the North-West Province which has both semi-urban and informal settlements. The hospital also receives many referrals from the other three districts namely, Ruth Segomotsi Mompati, Bojanala and Ngaka Modiri Molema. These areas span over 104 square kilometres with a population of four million people.

Given the bundle of care required for VLBW neonates, the NICU is the main area of focus for this study. The area is covered by one Paediatrician, one Paediatric registrar and two medical officers. The nursing staff consist of professional nurses at patient ratio of 2:1 and sometimes 3:1.

Consent

Approvals from the KH clinical manager and the WITS Human Research Ethics Committee were obtained; ethics approval number M170223.

Inclusion criteria

The patients included in the study were only neonates admitted to the KH NICU/ high care, weighing <1500g and born in the period between Jan 2015 and Dec 2016 (2 years). They were admitted within 24 hours of birth and those that died were less than 28 days of life. VLBW neonates admitted more than 24 hours after birth, admitted outside the NICU/high care were excluded. Deaths that occurred in the labour ward/theatre or beyond the first 28 days of life were also excluded.

Data collection

Files

Files were manually collected from both the records room (files of patients who survived) and the storage room (files of patients who died) with the help of an assistant. The aim was to collect as many files as were available. To this end, the collection was both opportunistic and random.

Data was de-identified and captured onto a password protected laptop to ensure patient confidentiality. All the information was captured using an excel datasheet. A total of 183 files that met the inclusion criteria were collected. One hundred were neonates that survived and 83 were those that died.

Figure 1 shows that of the 7 465 live births documented from the birth registries in the two-year period between January 2015 and December 2016. Of the 439 documented to be VLBW, only 174 files were found and manually collected from the records department, 72 did not meet the inclusion criteria and 10 had a significant amount of missing information. A final 183 files were obtained, 100 were of patients who survived and 83 were of those who died. Demographics of those with files not found could not be compared to those found.

PPIP forms

For every neonatal death that occurs a PPIP form is completed with final cause(s) of death and underlying factors noted. Modifiable factors are also recorded as they pertain to the maternal, obstetric, hospital administration and medical personnel categories. All deaths are discussed at Morbidity and Mortality (M&M) meetings held weekly by the Paediatric department at KH and chaired by a Paediatric consultant. Only 51 forms (61.4% of the death files collected) were found for review.

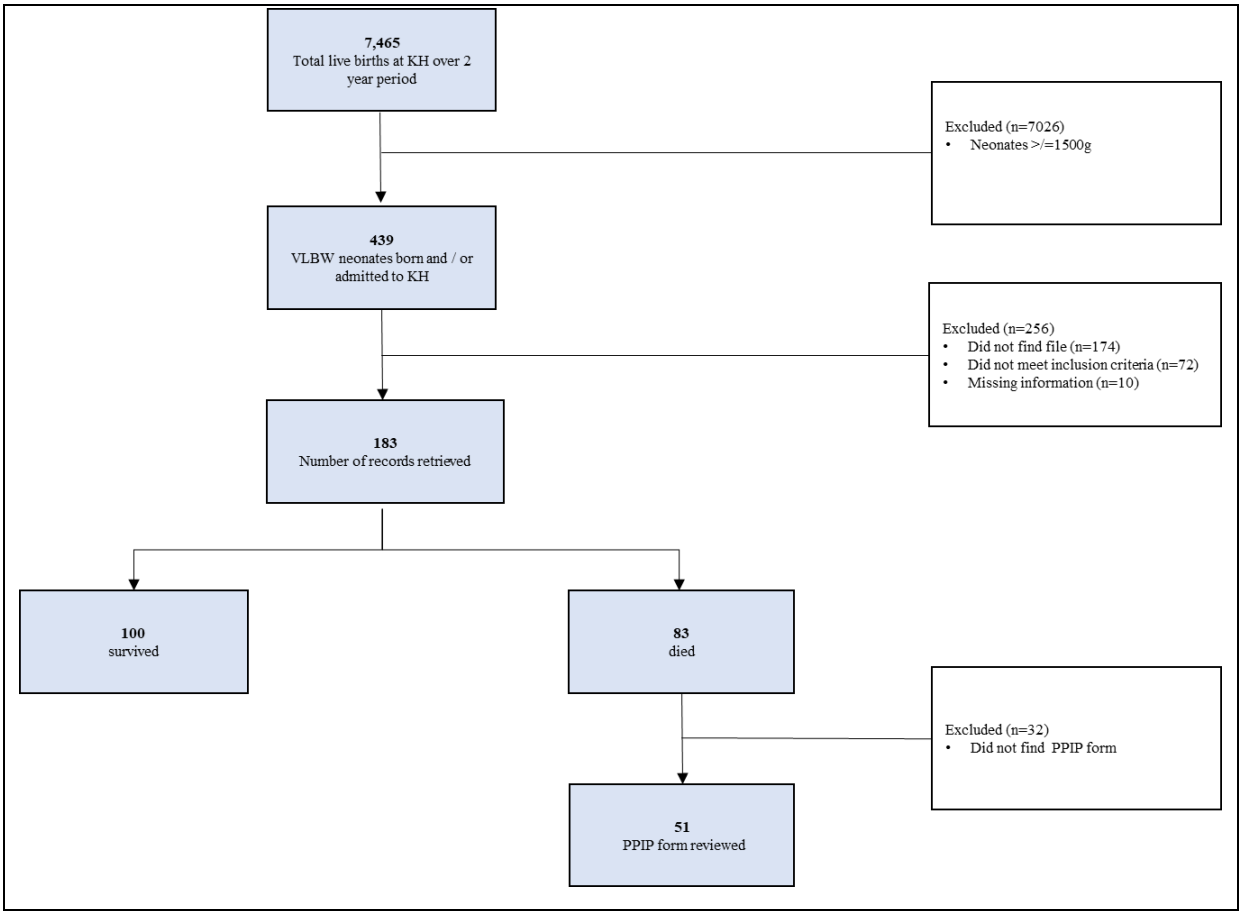

Figure 1. Breakdown of records collected.

Data analysis

Descriptive statistics were used to compare the demographics and characteristics of VLBW neonates using frequencies and percentages. To test each variable for its significance between those that died and survived, the Mann Whitney U test was used for continuous non-parametric variables and is expressed as medians and interquartile ranges. The chi-squared/ Fischer's exact two-tailed tests were used for categorical data and are expressed as p values.

Variables with a p value <0.1 from **Table 1** as well as those known to be significant from literature were used in the univariate analysis. The results from the univariate analysis show the association of each variable to the outcome that is death.

To better resemble real-life where neonates have multiple comorbidities simultaneously, the multivariate logistic regression was used. Variables chosen were those with a p value <0.1 from the univariate analysis. If the variables that had five or less observations in a group, they were excluded. Additionally, a backward stepwise regression was used to remove variables

with weak correlations. The results of the multivariate logistic regression are those that likely to predict death.

The univariate and multivariate analysis results are expressed as odds ratios, two-sided 95% confidence intervals, and associated p values.

Our null hypothesis (H_0) was, 'the comorbidity is *not* a predictor of death'. The alternative hypothesis (H_1) was, 'the comorbidity *is* a predictor of death'. We looked for evidence in our results to reject the H_0 in favour of the H_1 at a significance level of 0.05.

The analyses were run using STATA *version 16.1 StatCorp LCC (2019)* and STATISTICA *version 14.0 TIBCO StatSoft Inc (2021)*

Sample size estimations

It is known from the death registry that the proportion of deaths that occurred amongst VLBW neonates in the neonatal unit at KH during the two-year period was approximately 20% (104 of 439). The sample size used in the logistic regression consisted of 183 VLBW neonates; 83 that died and 100 that survived. The proportion of deaths is overrepresented at 45%. Thus, the study sample is not representative of the larger population. However, statistically the coefficient estimates are unbiased and thus variables that have an impact on outcome can be inferred.

The sample size requirements for significance in a logistic regression suggest ten cases for every one event per variable (10:1). In this study, the 'event' would be death. Given that there are 83 events, a maximum of eight variables can be used.

Results

The sample collected consists of 183 VLBW neonates, **Table 1**. shows their demographics and characteristics. The majority (55%) of mothers were between the ages of 20 and 34 years old. Sixteen percent were less than 20 years old with the youngest being 14 years old. Thirty-nine percent of mothers had preterm premature rupture of membranes. Fifty-seven percent of mothers delivered via caesarean section and more than two thirds (69%) did not receive antenatal steroids despite it being free and readily available. Seventy-eight percent of neonates were born less than 32 weeks gestation; the median gestation of those that died was lower compared to the median gestation of those that survived; 28 (IQR 24-32) vs 30 (IQR 27-33), p = 0.001. There is a statistically significant chance of death if born between 26 and

31 weeks gestation, p = 0.000. Most of the neonates (69%) were above the extremely low birthweight (ELBW) threshold (weighed >1 000g). The ELBW (weighed <1 000g) neonates had a higher proportion of deaths (54%).

The male to female ratio is almost equal at 0.9. It is not known how many patients received surfactant or ventilation, however it is noted that 64% were diagnosed with respiratory distress syndrome with similar numbers across those who survived and died. Other common complications/comorbidities of prematurity are noted and compared amongst those who died and survived. More unconventional comorbidities include metabolic acidosis and hypotension-requiring-inotropes as factors that both had significantly higher incidences amongst those who died, 59% compared to 14% and 44% compared to 6% respectively. Most babies are noted to have breastfed (49%) compared to those that formula fed (38%) and mixed fed (6%) and the number of babies diagnosed with NEC was 22% of which 12% died.

Of the VLBW neonates that died, 77% died in the first seven days of life and 40% within the first three days life.

Table 1. Demographics and characteristics of VLBW neonates based on death as an outcome.

Variables	**Total n =183**	**Survived n =100**	**Died n =83**	**p value**
	n (%)	**n (%)**	**n (%)**	
Maternal information				
Maternal age (years)				0.535
<20	30 (16)	15 (15)	15 (18)	
20-34	100 (55)	49 (49)	51 (61)	
>=35	19 (10)	12 (12)	7 (8)	
Missing	34 (18.5)	24 (24)	10 (12)	
Median	28	29	26	
Caesarean section	104 (57)	66 (66)	38 (46)	0.009
Missing	4 (2)	1 (1)	3 (4)	
Maternal pathology				
Cervical incompetence	1 (0.5)	1 (1)	0 (0)	1.000
No antenatal steroids	126 (69)	72 (72)	54 (65)	0.316
Infection	11 (6)	6 (6)	5 (6)	0.995
PPROM	71 (39)	47 (47)	24 (29)	0.012
IUGR	10 (10)	5 (5)	5 (6)	0.762
APH	14 (8)	5 (5)	9 (11)	0.139
Cardiac pathology	2 (1)	1 (1)	1 (1)	1.000
Neonatal information				
In-born at KH	146 (80)	78 (78)	67 (81)	0.510
Male	85 (46)	49 (49)	36 (43)	0.447
HIV exposure	68 (37)	40 (40)	28 (34)	0.383
APGAR^{1} <6	68 (37)	27 (27)	41 (49)	0.002
APGAR^{5} <6	43 (23)	17 (17)	26 (31)	0.022
Gestational age (weeks)				
<26	25 (14)	4 (4)	21 (25)	0.202
26-31	117 (64)	68 (68)	49 (59)	0.002
>=32	41 (22)	28 (28)	13 (16)	0.318
Total	183(100)	100 (100)	83 (100)	
Median (IQR)	29 (27-31)	30 (27-33)	28 (24-32)	0.001
Birthweight (g)				
<1 000	56 (31)	11 (11)	45 (54)	0.000
>=1 000	127 (69)	89 (89)	38 (46)	0.000
Total	183(100)	100 (100)	83 (100)	
Median (IQR)	1170 (830-1510)	1265 (1005-1525)	980 (665-1295)	0.000

Age at death (days)				
<4	33 (40)		33 (40)	
4-7	31 (37)		31 (37)	
>7	19 (23)		19 (23)	
Total	83 (100)		83 (100)	
Neonatal pathology				
RDS	118 (64)	60 (60)	58 (70)	0.164
Sepsis	79 (43)	45 (45)	34 (41)	0.586
Metabolic acidosis	63 (34)	14 (14)	49 (59)	0.000
Hypotension-requiring-inotropes	43 (23)	6 (6)	37 (44)	0.000
Pulmonary haemorrhage	25 (14)	0 (0)	25 (30)	0.000
IVH	18 (10)	5 (5)	13 (16)	0.016
Anaemia requiring blood transfusion	69 (37)	39 (39)	30 (36)	0.692
Renal dysfunction	45 (25)	13 (13)	32 (39)	0.000
Asphyxia	16 (9)	3 (3)	13 (16)	0.003
Hypothermia	13 (7)	1 (1)	12 (14)	0.000
Hypoglycaemia	22 (12)	8 (8)	14 (17)	0.066
Hyperglycaemia	22 (12)	7 (7)	15 (18)	0.022
PDA	27 (15)	24 (24)	3 (4)	0.000
NEC	41 (22)	31 (31)	10 (12)	0.002
Feeding				0.000
Formula	69 (38)	64 (64)	5 (6)	
Breast milk	90 (49)	31 (31)	59 (71)	
Mixed	5 (3)	5 (5)	0 (0)	
Total	164 (90)	100 (100)	64 (77)	
Missing	19 (10)	0 (0)	19 (23)	
Congenital abnormality	5 (3)	2 (2)	3 (4)	0.660

PPROM, preterm premature rupture of membranes; IUGR, intrauterine growth restriction; APH, antepartum haemorrhage; KH, Klerksdorp Hospital; HIV, human immunodeficiency virus; APGAR[1], Virginia Apgar score at one minute; APGAR[5,] Virginia Apgar score at five minutes; IQR, interquartile range; RDS, Respiratory distress syndrome; IVH, interventricular haemorrhage; PDA, patent ductus arteriosus; NEC, necrotising enterocolitis.

Table 2. Causes of death from PPIP audit	
Causes of death	**n = 51**
Final Cause of death	**n (%)**
Sepsis	12 (24)
Extreme multi-organ immaturity	10 (20)
Pulmonary haemorrhage	10 (20)
RDS	6 (12)
IVH	4 (8)
NEC	3 (6)
Asphyxia	2 (4)
Obstetric cause of death	
PPROM	12 (24)
Eclampsia	8 (16)
Proteinuric hypertension	2 (4)
Placenta previa	2 (4)

RDS, respiratory distress syndrome; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PPROM, preterm premature rupture of membranes

Table 3. Modifiable factors from PPIP audit	
Modifiable factors	**n =51**
Medical	**n (%)**
Nosocomial infection	9 (18)
Insufficient notes	8 (16)
Antenatal steroids not given	3 (6)
Administrative	
Personnel not sufficiently trained to manage the patient	3(6)
Other administrative problems (power failure)	3 (6)
No response to history of stillbirths, abruptio etc.	2 (4)
Maternal	
Never initiated antenatal care	6 (12)
Delay in seeking medical attention during labour	3 (6)
Booked late in pregnancy	2 (4)

The PPIP form audit in **Table 2** shows the common final causes of death to be sepsis (24%), extreme-multiorgan prematurity (20%) and pulmonary haemorrhage (20%) which is a complication of extreme multiorgan prematurity. Here sepsis is not categorised as early/late or congenital/acquired because positive blood cultures were not always available to confirm suspicions / inferences on cause. As such, both are combined as 'sepsis'.

The two main obstetric-related causes of death were PPROM (24%) and Eclampsia (18%).

Table 3 shows modifiable factors separated into medical, administrative, and maternal subcategories, with the top 3 factors noted in each. The most common was the prevention of nosocomial sepsis (18%).

Table 4. Univariate logistic regression showing the association between each variable and the outcome of death.

Variable	**Univariate analysis OR (95% CI)**	**p value**
No antenatal steroids	1.381(0.737-2.587)	0.313
Caesarean section*	0.452 (0.247-0.829)	0.010
Male	0.797 (0.444-1.430)	0.448
APGAR[1] <6*	2.369 (1.424-4.889)	0.002
APGAR[5] <6*	2.227 (1.2107-4.476)	0.025
Gestational age (weeks)*	0.719 (0.617-0.837)	0.000
Birthweight (g)*	0.994 (0.992-0.996)	0.000
Sepsis	0.848 (0.470-1.527)	0.583
Metabolic acidosis*	8.852 (4.333-18.087)	0.000
Hypotension-requiring-inotropes*	12.60 (4.962-31.999)	0.000
Pulmonary haemorrhage‡		
IVH† (all grades)	3.528 (1.202-10.355)	0.022
Renal dysfunction* (unspecified)	4.199 (2.020-8.726)	0.000
Asphyxia†	6.004 (1.648-21.867)	0.007
Hypothermia†	16.732 (2.126-131.628)	0.007
Hypoglycaemia†	2.333 (0.927-5.872)	0.072
Hyperglycaemia*	2.930 (1.133-7.578)	0.027
PDA	0.118 (0.3434-4.106)	0.001
NEC*	0.304 (0.139-0.668)	0.003
Feeding‡		

APGAR[1], Virginia Apgar score at one minute; APGAR[5], Virginia Apgar score at five minutes; IVH, interventricular haemorrhage; PDA, patent ductus arteriosus; NEC, necrotising enterocolitis
*, p value <0.1 and added to multivariate logistic regression; †, had between one and five observations in a survived/died group; ‡, had zero observations in either the survived/died group

Results from the univariate regression analysis in **Table 4** show variables (in isolation) and their association with death.

Asphyxia, hypothermia and IVH had less than six neonates in the 'Survived' or 'Demised' group and as such the results may not be reliable. PDA has its confidence intervals extending on both side of 1, thus is not significant.

Statistically significant factors that were protective against death were caesarean section, high gestational age, increasing birthweight and necrotising enterocolitis (NEC) which is unusual.

Table 5. Multivariate logistic regression showing predictors of death

Variable	**multivariate analysis OR adjusted (95% CI)**	**p value**
Birthweight (g)	0.993 (0.989-0.996)	0.000
Metabolic acidosis	17.785 (4.711-67.145)	0.000
Hypotension-requiring-inotropes	26.074 (5.403-125.827)	0.000

The results from the multivariate logistic regression in **Table 5** showed the two predictors of death to be metabolic acidosis and hypotension-requiring-inotropes. An increase in birthweight was shown to be protective against death.

Discussion

Forty-five percent of the under-five mortality rate (U5MR) is attributed to neonatal deaths globally.[10] Of these deaths, prematurity and specifically VLBW neonates (<1500g) account for the biggest proportion. [6] KH had neonatal mortality rates (NMR) of 25.4/1 000 and 39.5/1 000 live births in 2015 and 2016, respectively. These were well above the South African national NMR of 11/1000 at the time. [10] The numbers are however comparable to South-East Asia and sub-Saharan Africa (26.2 and 26.9/1 000 respectively).[2] A rural district hospital in Kwazulu-Natal showed preterm delivery and extremely low birthweight neonates as key predictors of death, which is expected. [11] What is often unclear is what aspects within prematurity result in death? To answer this question, the results from this study show both the subjective opinion of experienced doctors in the form of the PIPP audit as well as the objective factors/ comorbidities that show a predictive value on the outcome of VLBW neonates.

The results from the PPIP audit showed the final causes of death to be i) sepsis (24%), ii) extreme multi-organ prematurity (20%) and iii) pulmonary haemorrhage (20%). This is comparable to a study looking at VLBW mortality at Chris Hani Baragwanath Hospital (tertiary level), it showed the top three causes of death to be immaturity, sepsis and RDS [6] There is a huge difference in mortality rate in the UK compared to lower-middle-income countries due to better resources and access to health care services.[12] The main causes of neonatal deaths are attributed to low birthweight and congenital abnormalities. [12]

Studies in South Africa have sepsis and prematurity among common causes of admission, suggesting that sepsis is a common comorbidity amongst VLBW neonates. [11, 13] This study also highlights sepsis as a common comorbidity amongst those who survived and died (45% vs 43%). In keeping with this, the univariate logistic regression did not show sepsis to be a significant predictor of death. What is clear is that sepsis complicated with hypotension and metabolic acidosis (septic shock) is associated with increased mortality. A study by Schindler et al. had sepsis as the 3rd leading cause of death amongst premature neonates.[14] When looking closely at the associated variables; an acidosis with a pH of less than seven was present in 47% of those with sepsis that died compared to only 17% of those with sepsis who survived.[14] Thus the presence of a metabolic acidosis and hypotension-requiring-inotropes are better representatives for sepsis complicated by shock.

Results in **Table 1** show the majority of deaths (54%) occurred in neonates with a median weight of 980g (IQR 665g-1295g). It stands to reason that the lower the birthweight or gestation, the higher the risk of death. [6, 11, 14] This study supports this by illustrating that for every unit increase in weight or gestation there is a reduction in the odds of dying, 0.994 and 0.719 respectively. When looking at adjusted ratios in the multivariate logistic regression, only an increase in birthweight was protective against death. This may be accounted for by correlation (r 0.559) between birthweight and gestation. It also suggests that birthweight is a better representative for prematurity given the inaccuracies of calculating gestational age in a setting of unsure dates and late antenatal bookings.[6]

All the neonates that had pulmonary haemorrhage (PH) in this study died (100% mortality rate). They were all ventilated and as per protocol received adrenaline via the endotracheal tube. A study by Ahmed et al showed high fatality of PH in neonates <28 weeks gestation within the first seven days of life. [15] Significant associations with early PH were surfactant (Curosef) administration, shock and IVH. [15] Other factors from **Table 4** that had significant

predictive values on death were renal dysfunction and hyperglycaemia. It can be inferred that these factors associated with compromised perfusion increase the risk of death and are most likely to occur in the presence of septic shock. [15, 16]

It is not clear why NEC was found to be protective against death. NEC in this study is not specified and includes all clinical grades of Bell's Criteria. Two plausible explanations are that i) most of the cases were suspected NEC based on clinical suspicion and ii) if confirmed, all cases of NEC would have been pre-emptively treated as 'sepsis' early enough to mitigate compromised perfusion and subsequent death.

Respiratory distress syndrome (RDS) is present in 64% of the neonates, with 70% being those who died. The high prevalence in those that died in spite of access to both NCPAP and surfactant suggests inadequate antenatal steroids. Mwansa-Kambafwile et al highlighted RDS as the most common cause of death in neonates <32 weeks and in low-income countries.[17] It is noted that even if only one dose of antenatal steroids is given <24 hours before delivery, there can be a reduction in mortality of up to 47%.[17]
Low one and five-minute APGARs and asphyxia when adjusted were not found to be predictors of death in this study. However, a retrospective cohort study by Gopagondanahalli et al, highlighted premature hypoxic-ischaemic encephalopathy and its neurological sequalae. [18] In addition, they showed that a one-minute APGAR less than five, a five-minute APGAR less than seven, a metabolic acidosis with a pH less than seven and major resuscitation were associated with death.[18]

The main obstetric causes of death were preterm premature rupture of membranes (24%) and eclampsia (16%). A South African study looking at maternal and perinatal outcomes in women with pre-eclampsia showed that it is associated with premature delivery and increased perinatal mortality.[19] Allanson et al. showed that maternal complications such as spontaneous premature labour contribute significantly to neonatal deaths. [12]. The study recommends improving diagnosis and management of preterm labour, particularly the use of antenatal corticosteroids. [20] Most mothers to the VLBW neonates in this study were more likely to have an emergency caesarean section (108 of 183) which was shown to be protective against death and is supported in other studies for better outcomes in both neonate and mother. [6,11]

Table 3 shows the two common maternal modifiable factors were, i) not initiating antenatal steroids and ii) delays in seeking medical care. The most probable reason for these challenges was poor timely access to health care services. For a considerable proportion of the community who live in remote areas and fall in the poor socio-economic stratum, access to transport and access to health facilities is both difficult and expensive.[13] By contrast, a UK audit of deaths in premature neonates had no maternal modifiable factors which speaks to better access to health care in high income countries. [7]

Administrative modifiable factors at KH were inadequate facilities, and insufficient trained medical staff. Rhoda et al echoed similar findings as their top modifiable factors included the lack of NICU beds with ventilators, insufficient nurses on duty, lack of transport to a health care facility and inadequate facilities.[13]

Insufficient staff in the form of professional nurses meant that the NICU with eight beds was, in some instances, cared for by one professional nurse and three nursing assistants. This was exacerbated by the fact that the nursing assistants were not adequately trained to assist with lifesaving procedures.

Common medical modifiable factors were nosocomial sepsis and failure to provide antenatal steroids. Nosocomial sepsis suggests that most of the sepsis suspected was late onset and thus a consequence of poor infection control. This may be exacerbated by staff shortages and lax enforcement. This is a common problem in several public hospitals that are overrun with patients and have a strained workforce of nurses and doctors. The most likely reasons for the non-provision of antenatal steroids were that expectant mothers didn't attend antenatal follow-ups and presented late to the hospital. This is a function of poor education of mothers and inherent systemic issues of inter healthcare access and transportation to health care facilities. [10,13]. The paucity of information in some files was attributed to incomplete patient transfer/referral letters and incomplete documentation of patient notes by in-house doctors. This has significant implications on the accuracy of patient diagnoses and understanding risk factors, complications and outcomes.

Limitations of study

There was a big proportion of files missing. Files collected were only of those that were admitted and died in NICU/high care. Any deaths that occurred in the labour ward or theatre are not included in this sample. Of the 83 that died, only 51 PPIP forms were found thus rendering the findings inconclusive.

The proportion of VLBW neonates that survived was underrepresented in the sample collected (100 of a possible 345) compared to the proportion of those that died (83 of a possible 104). This meant that the study sample was not representative of the larger population. For this reason, issues of external validity exist.

Recommendations

It is recommended that patient records be digitalised for easier access. It is imperative that adequate history taking, and the documentation of care be meticulous. This will allow for more accurate record keeping which can be used for future studies. Improvement in infection prevention control (IPC) and antimicrobial stewardship programmes. Promoting antenatal care and early bookings and administration of antenatal steroids. Referrals to tertiary facilities for better management of high-risk pregnancies. The use of NCPAP and surfactant.

Conclusion

VLBW neonates are at an increased risk of death within their first week of life from septic shock. Their vulnerability lies in their prematurity which lends itself to immature organ systems and very little reserves. Strategies to improving neonatal outcomes lie in improving quality of healthcare provided to both mother and baby. Primarily better IPC measures and audits should be implemented to decrease sepsis. Furthermore, the use of quality care audits and regular data monitoring are essential components of addressing and reducing neonatal mortality.

Acknowledgements

We thank all the health care workers who care for the patients and the hospital management team for giving permission to conduct the research. The authors wish to acknowledge Professor S.Velaphi and Professor D. Ballot for their invaluable advice and express our sincere gratitude to Professor K. Thandrayen and Boikanyo Mothibatsela for their assistance with the biostatistics.

Author contributions NM: protocol, data collection, write-up; LC and OM: oversight, advice, and editing.

Funding. None.

Conflict of Interest. None declared.

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Appendices

Appendix A Letter of authorisation from Hospital

Appendix B Ethics clearance letter

Appendix C Research protocol

Appendix D Master-sheet

Appendix E PPIP forms

Appendix F Plagiarism declaration

Appendix G Turnitin report

Appendix H Author guidelines SAJCH

Appendix A Letter of authorisation from Klerksdorp Hospital

health
Department of
Health
North West Province
REPUBLIC OF SOUTH AFRICA

All correspondence to be directed to:
The Hospital Board
Clinical Manager
K/T Hospital Complex
Private Bag A14
KLERKSDORP
2570

Tel: (018) 406 4749
Fax: (018) 462 5923
Enq: sbool@nwpg.gov.za

CLINICAL MANAGER'S OFFICE

18th November 2016

To whom it may concern

Dear Sir/ Madam

RE : APPROVAL OF THE RESEARCH

This letter serves to confirm that approval has been granted to Dr. Mwala by the Patients Safety Group that was held on the 13th October 2016 at PSG Klerksdorp/Tshepong Hospital Complex.
The primary objective of the research is to reduce the neonatal mortality rate at Klerksdorp Hospital with the following secondary objectives

1. To determine significant, common causes of death in neonates weighing <1500g between January 2014 and December 2016
2. Determining key modifiable and workable solutions that could significantly improve the prospects for these neonates.

The study is a retrospective cohort observational study.

Hope that you find the above in order.

.....
Dr. N. D. Leburu
Clinical Manager
K/T Hospital Complex

Healthy Living for All

1

Appendix B Ethics clearance letter

R14/49 Dr Nalishebo Mwala

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170223

NAME: (Principal Investigator)	Dr Nalishebo Mwala
DEPARTMENT:	Paediatrics Klerksdorp Hospital
PROJECT TITLE:	A Study to Determine the Causes of Death in Neonates Weighing <1500g at Klerksdorp Hospital
DATE CONSIDERED:	24/02/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Mekgoe and Dr Chirwa
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/03/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C Research Protocol

Research Protocol

November 2016

By: Dr N Mwala MBBCh (WITS) DCH(SA)
Student no. 0702307F
Registrar in the Department of Paediatrics, Wits
Supervisors:
Dr Mekgoe MBChB, FCPaed (SA)
Dr Chirwa MBBCh, FCPaed (SA) Cert. Neonatology (SA)

Research Topic

A study to determine the causes of death in neonates weighing <1500g at Klerksdorp Hospital

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List of abbreviations

APH	Antepartum Haemorrhage
COD	Cause of Death
ELBW	Extremely Low Birthweight
HGT	Haemo Glucose Test
HIE	Hypoxic Ischaemic Encephalopathy
HMD	Hyaline membrane disease
IUGR	Intrauterine Growth restriction
IVH	Intraventricular Haemorrhage
LBW	Low Birthweight
MAS	Meconium Aspirations Syndrome
MDG	Millennium Development Goals
NCPAP	Nasal Continuous Positive Airway Pressure
NHLS	National Health Laboratory Service
NICU	Neonatal Intensive Care Unit
NMR	Neonatal Mortality Rate
NNE	Neonatal Encephalopathy
PH	Pulmonary Haemorrhage
PMTCT	Prevention of Mother to Child Transmission
PPIP	Perinatal Problem Identification Program
PPROM	Preterm Premature Rupture of Membranes
RDS	Respiratory Distress Syndrome
SDG	Sustainable Development Goals
UN	United Nations
U5MR	Under Five Mortality Rate
UNICEF	United Nations Children’s Fund
VLBW	Very Low Birthweight
WHO	World Health organisation

Definitions

Anaemia	haemoglobin usually <10 or level at which the patient becomes symptomatic requiring a blood transfusion
Early neonatal death	death occurring between 0 - 7 days of life
ELBW	neonates with a birthweight of <1000g
Hyperglycaemia	an HGT >11.1
Hypoglycaemia	an HGT < 2.6
Hypotension	a low blood pressure at which perfusion is compromised and inotropes are required
Hypothermia	a temperature < 36.5
Late neonatal death	death occurring between 7 - 28 days of life
LBW	neonates with a birthweight of 1500-2500g
Metabolic acidosis	a pH <7.25, HCO3 <15 and BE <5
PDA	based on clinical suspicion with a wide pulse pressure and a cardiac murmur (Echo confirmation not always possible)
Pulmonary haemorrhage	acute bleeding from the lung/respiratory tract usually noted as fresh blood in the endotracheal tube resulting in haemodynamic instability and respiratory failure
Renal dysfunction	any deviation from normal values based on NHLS parameters
Congenital infection	for the purposes of this study this was defined as either a confirmed positive culture taken within the 1st 3 days of life or suspected infection based on maternal history and/or clinical suspicion and/or biochemical markers
Nosocomial infection	for the purposes of this study this was defined as a positive culture after 3 days of life or suspected infection based on history and/or clinical suspicion and/or biochemical markers

Introduction

In 2000, 189 UN member nations adopted 8 millennium development goals (MDGs) to reduce extreme poverty in its many dimensions (Millennium Developmental Goals, 2016). Amongst the 8 MDGs is a commitment to “Reduce child mortality”. The aim was to reduce the NMR globally by two thirds from 21/1000 in 1990 to 7/1000 live births by 2015 (8).

This mammoth task has proven difficult to achieve. Reflecting on the stagnant NMR levels, the WHO and UNICEF revised global targets through the articulation of the ‘Every New-born’ action plan in 2014; a plan to reduce NMR to 7/1000 deaths by 2035 (vs. earlier MDG targets of achieving these levels by 2015) (9). To achieve this, several basic interventions have been explored to ultimately improve the quality of health care provided to mothers and their babies. These interventions include empowering communities, forming partnerships, increasing healthcare coverage, and improving the quality of health care (9).

Similarly at the broader UN level, the Sustainable Development Goals (SDGs) have subsequently succeeded the Millennium Development Goals (MDGs) as of 2015. They consist of 17 goals to eliminate extreme poverty by 2030. Like the MDGs the 3rd SDG goal pertaining to “Good Health and well-being” echoes the same sentiment to ensure better quality health care and improved survival rates of neonates. (2). It aims to reduce the NMR and the U5MR to <12/1000 and <25/1000 live births respectively (2).

A study conducted at Chris Hani Baragwanath Academic Hospital highlighted the challenge (7). Between 2000 and 2002, very low birthweight (VLBW) babies accounted for only 3% of their total live births and yet formed 20% of their admissions and 55% of their deaths (7). Furthermore, as highlighted by Lloyd and De Witt, very little progress had been made in sub-Saharan Africa in achieving the desired reduction (3). Statistics South Africa 2014 illustrate a marginal NMR reduction of 46/1000 to 36/1000 lives births between 1990 and 2013 respectively (10). In South Africa specifically the NMR in 2009 was still at a high of 19/1000 live births with most of these deaths occurring in neonates weighing less than 1500g, well short of the7/1000 per live births target (3).

The continuing challenge of neonatal mortality in neonates weighing less than 1500g in South African hospitals highlights the need to better understand the causes of these deaths as well as their associated modifiable factors.

Further stratifying the data into early versus late neonatal deaths will help to unveil a predilection to different vulnerabilities and highlight different key causes of death and modifiable factors. The Saving Babies 2010 - 2011 report reflects the early neonatal death rate as 21/1 000 live births, with the majority of these deaths occurring in the 1000-1499 g weight category (4). 40% of these deaths were attributed to prematurity and 23% to complications of birth asphyxia. Most of the deaths when reviewed in the Perinatal Problem Identification Programme (PPIP) where thought to be preventable (4).

A 2015 article by D. E Ballot et al based on a study done at Charlotte Maxeke Academic Hospital validates the need to keep reviewing the outcomes of our neonates (1). The retrospective review compared the morbidity and mortality of infants weighing less than 1500g between 2006/2007 and 2013 (1). The results indicated how changes in

interventions/protocols can significantly improve the survival rates of neonates. For example, the use of early surfactant therapy and increased use of NCPAP have significantly improved survival rates by up to 30% in the 750g-900g weight category (1).

The study objectives of this study are to identify the most vulnerable group of neonates and develop workable solutions to improve their mortality rates. The UN and WHO provide a helpful framework and context for this study. It is evident from specific health improvement goals set out by the member nations that improvements have been less than ideal, and that action needs to be taken right away. The Northwest has been identified as the province with the 5th highest neonatal mortality rate (NMR) in South Africa at 8.8% (6). Within the Northwest in 2015, Klerksdorp hospital had an NMR of 31.3/1000 live births. The neonates weighing between 500-999g and 1000-1499g had mortality rates of 846.2/1000 live births and 330/1000 lives births respectively.

This study hopes to tease out the key modifiable factors with the use of the Perinatal Problem Identification Programme. It is a South African audit which considers both obstetric and neonatal avoidable factors (1).

It is envisaged that Klerksdorp Hospital will serve as a microcosm for other secondary level hospitals in developing countries in unpacking the contributing factors and workable solutions that help guide hospital guidelines and standard operating procedures to reduce NMRs.

Objectives

Primary objectives

1. To determine the causes of death and the factors that contribute to the deaths of neonates weighing less than 1500g at Klerksdorp hospital

Secondary Objective

1. To tease out key modifiable factors to improve the survival of neonates weighing less than 1500g at Klerksdorp hospital.

Methods

Study Design

Quantitative retrospective study that is based on the review of medical records of patients who meet the inclusion criteria.

Study site/population

Klerksdorp hospital is an academic hospital affiliated with The University of The Witwatersrand. It is classified as a secondary hospital, although it does offer some level 3 services. The Neonatal Unit consists of 40 beds of which 9 are high care beds and 8 are NICU beds. NICU provides respiratory support in the form of mechanical ventilation and CPAP (continuous positive airway pressure) as well as inotropic support. High care is for sick babies who do not require ventilator or inotropic support.

Patients admitted to Klerksdorp hospital are mainly from within the Kenneth Kaunda district of the Northwest Province which has both a semi-urban and informal settlements. The hospital also receives many referrals from the Dr Ruth Segomotsi Mompati district which is mainly rural and less frequently the other 2 districts namely Bojanala and Ngaka Modiri Molema.

The staff consist of 2 full time consultants (one of whom is the Head of Department), 1 sessional consultant and 2 consultants who assist with overtime calls. In addition to this are 2 registrars from the WITS main circuit who rotate throughout the year for two months at a time, 6 medical officers and 14 to 16 students who are divided between the different paediatric areas.

There are no subspecialists at Klerksdorp hospital and all complicated cases are either discussed and managed in consultation with subspecialists in the WITS circuit or simply transferred to either Chris Hani Baragwanath Academic Hospital or Charlotte Maxeke Academic Hospital.

The neonatal unit and specifically NICU and high care are the main areas of focus for this study. The area is covered by one consultant, 1 registrar and 2 medical officers. There are no interns allocated to NICU or high care, however 2 interns are allocated to the neonatal ward.

The nursing staff consists of 2 professional nurses and 2 nurses in ICU and 1 professional nurse and 1 nurse in high care.

The equipment available for our neonates includes; incubators and radiant warmers, phototherapy machines, ABG (arterial blood gas) machine, sonar machine, CT scanner, 1 bubble CPAP machine, 1 CPAP machine, 4 conventional ventilators and 2 high frequency ventilators. We have an onsite NHLS laboratory that does most of the investigations onsite with more specialised tests done in either Potchefstroom, Johannesburg, or Cape Town.

Inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
✓ Neonates admitted to the neonatal unit between Jan 2015 and Dec 2016 ✓ Referrals from within the Northwest province ✓ Birthweight <1500g ✓ Death occurring within the neonatal period in the NICU/ high care ✓ Alive upon discharge from the NICU/high care during the neonatal period	× Referral from outside of the Northwest province × Admission to Klerksdorp hospital after day 1 of life × Birthweight equal to or more than 1500g × Death occurring beyond neonatal period (>28 days of life) or outside the NICU × Files with incomplete or missing notes × Missing PPIP forms

Limitations

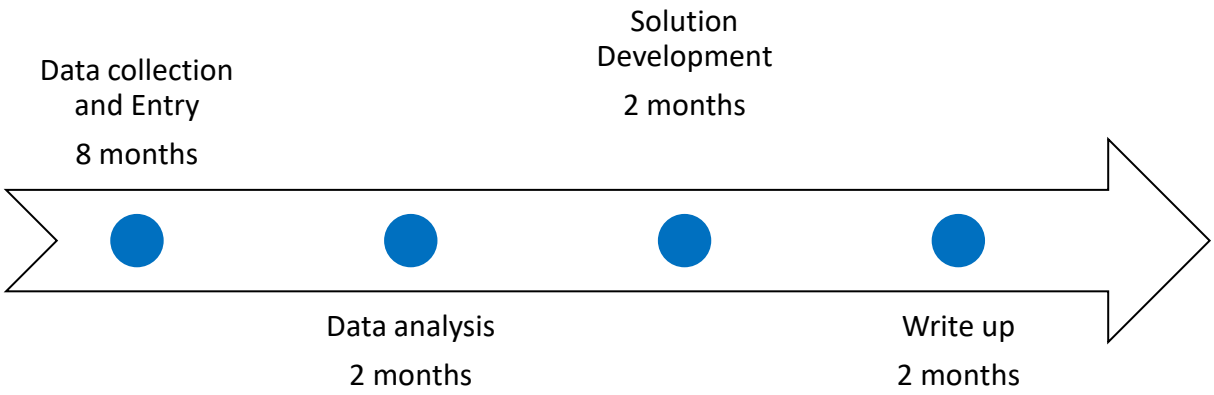
The study is heavily reliant on patient files and the corresponding PPIP forms for those who died, and the quality/completeness of notes may be variable.

Enrolment and Recruitment

Recruitment of participants into the study is based purely on patient records that meet the inclusion criteria.

Research Timeline

The research should be completed within 14 months. It will be based on ensuring dedicated time outside of working hours and other work responsibilities.

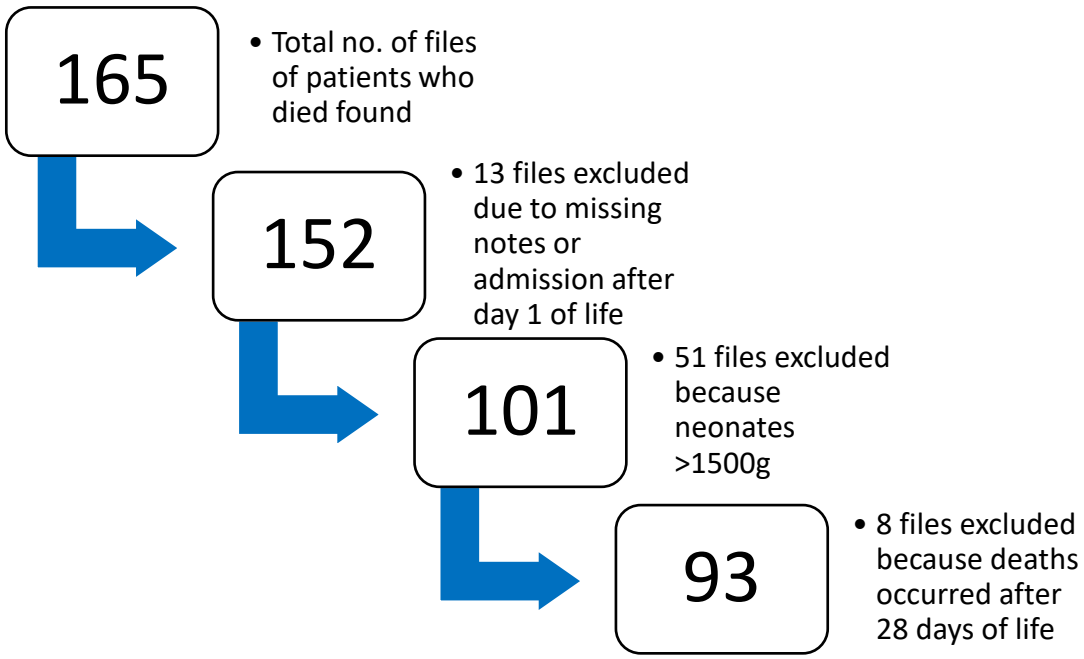


Data Collection and Entry

The data will be collected in "two groups"; the first will be a list of the neonates that were born and died between January 2015 and December 2016. A list of these neonates will be obtained from the data capturers on site at Klerksdorp hospital. This list will be given to a designated staff member at the records department who will locate the files and I will personally sign them out and back in.

The second group of files will be based on a list of all the neonates that survived their NICU/ high care admission. This list will be obtained from the NICU/high care registry. Similarly, this list will be given to a designated staff member in the records department to find. Because these files may be of potential current patients (either inpatient/outpatient) they will not be signed out for more than one day. Depending on the number of deaths that are collected for analysis a similar number of alive patients be collected as the control.

All data collected from the files will be entered into an excel database/master sheet. Files with incomplete information for adequate analysis or files with information that do not meet the inclusion criteria will be excluded.



The above diagram illustrates the number files of patients who died that will be used in this study (based on the WITS ethics approval from 2016).
*A similar number of files (93) will be collected of patients who survived (and meet the inclusion criteria) to be used as a control for this study.

Data Analysis

The data analysis will be done in Excel using formulas and pivot tables.

Appendix D is the master sheet for the data of the VLBW neonates.

The data will consist mainly of nominal categorical data. Formulas such as ‘Countifs’ and ‘Counta’ will be used to stratify the data variables. These will be used for comparative analysis and inferences, including but not limited to early vs late neonatal death, at which weight category most deaths occur (Microrem <500g; ELBW 500-999g and VLBW 1000-1499g), maternal demographics and associated factors such as antenatal steroids given, HIV exposure and maternal illnesses.

This nominal categorical data can be represented in the form of pie charts, bar graphs and histograms (5).

PPIP forms are completed for every death that occurs in the department at Klerksdorp hospital. They are completed after the case is presented at a Morbidity and Mortality (M&M) meeting attended by the entire department. The cause(s) of death is/are discussed as well as all modifiable factors pertaining to maternal and obstetric factors, and avoidable factors namely, administrative, patient, and medical associated.

Pivot tables will help demonstrate associations between maternal, obstetric, and patient factors. To determine the validity of the findings from the neonates that died, they will be compared to those that who survived, thus the strength of association will be determined by correlation analyses with the control group

Assumptions

Sepsis will be the leading cause of death in neonates weighing less than 1500g.

Solution development

To use key findings to find implementable solutions to reduce the neonatal mortality rate.

Data Safety and Monitoring

- All files will be handled within the confines of Klerksdorp hospital
- Permission by the head of neonates, Dr Mekgoe, has been obtained to use her office
- The files will be signed out and signed back in by myself
- No duplicates of the files will be made
- No names will be used to maintain patient confidentiality. All patients will be allocated a study number in the data collection sheet which will be stored on a personal computer with password security
- Me, my supervisors, and a designated statistician will have access to the database.

Ethics

Risks and benefits

There are no foreseeable risks in carrying out this research. On the other hand, the benefits are great. This research will provide Klerksdorp with baseline information regarding the NMR; it will unveil gaps in the health care provided as well as solutions to bridge those gaps. In the years to come the information can be used as baseline research upon which progress is noted and strategic guidelines are made.

Informed consent

Permission to proceed with the study has been granted from the clinical manager at Klerksdorp Hospital. This allows access to specified patient records and their accompanying PPIP forms.

Privacy and confidentiality

The privacy and confidentiality of patients' details and their families will be upheld. The families will not be contacted for further information beyond what is contained within the files. The database will make use of an allocated study number for each file.
The information contained within the files and database will be kept confidential as mentioned under "Data Safety and Monitoring".

Research Budget

The costs will by and large be incurred by myself. The hospital will endeavour to assist where possible.

	Description	**Total (ZAR)**
	Printing & stationary	1500
	Petrol to travel between Johannesburg and Klerksdorp	1500
Grand total		**3000**

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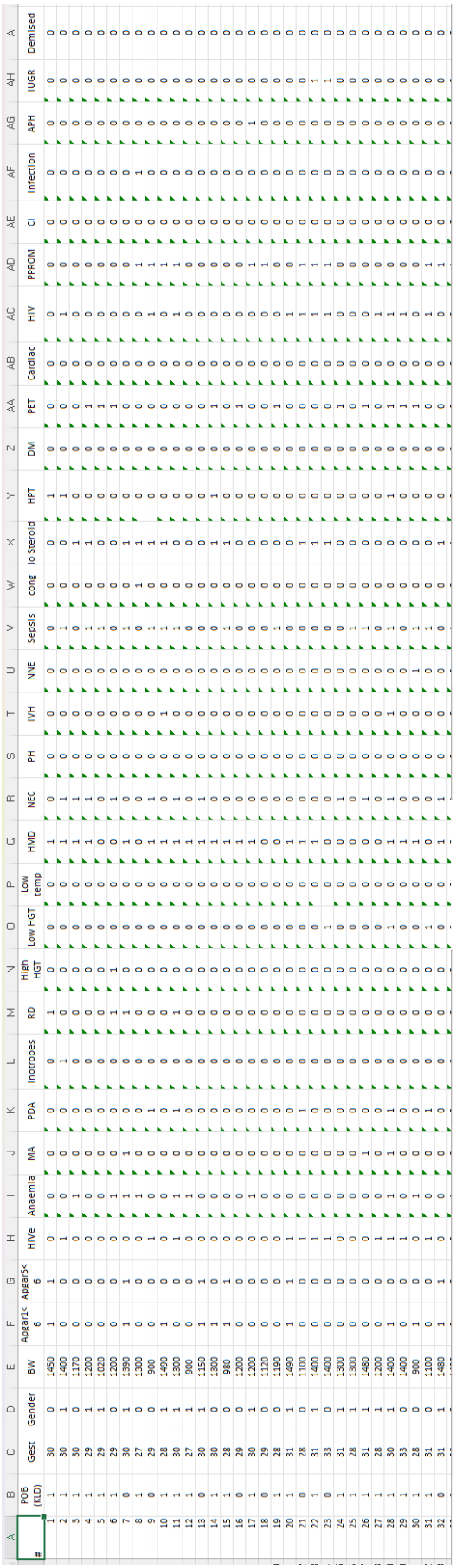
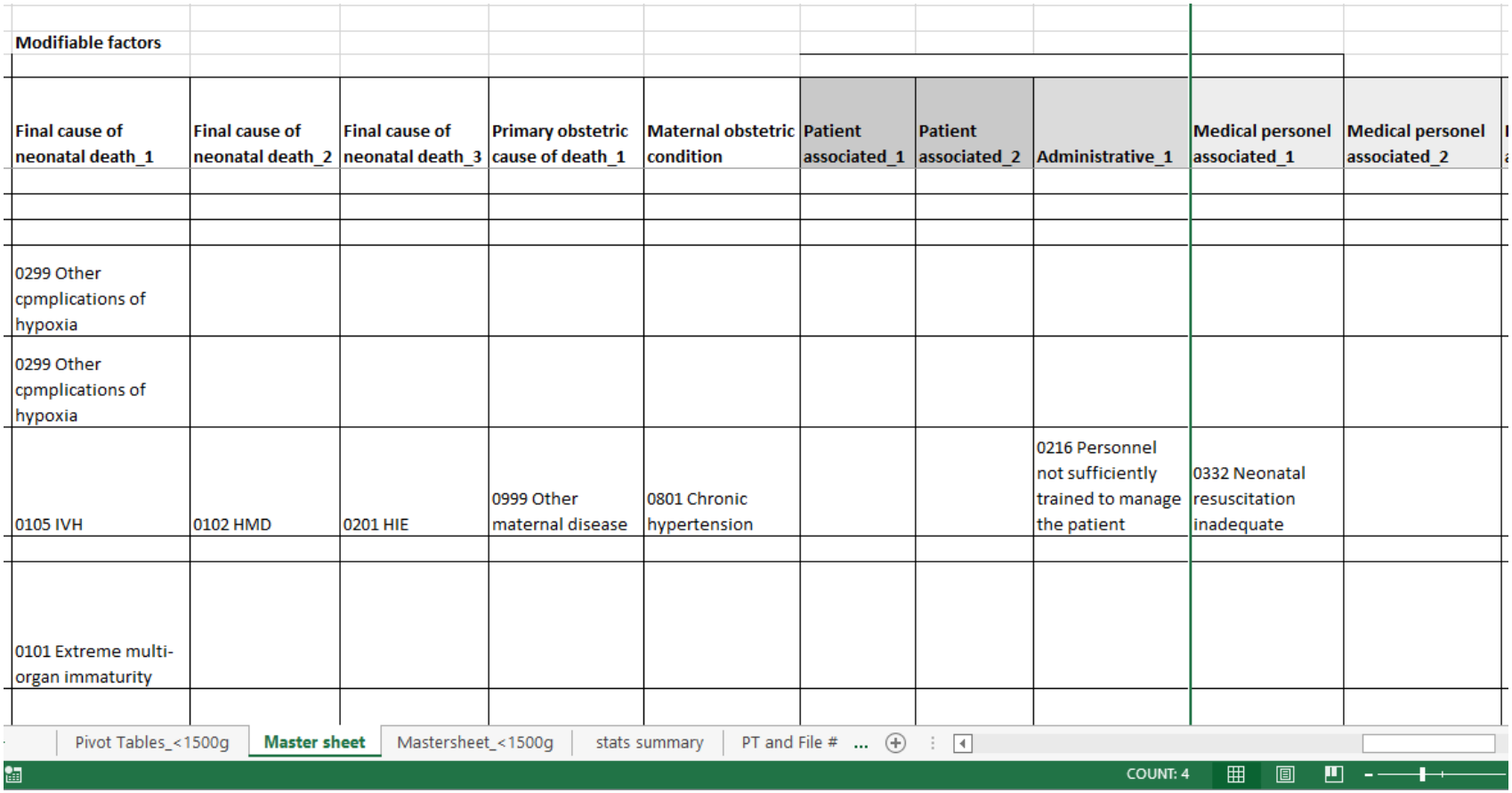
Appendix D Master-sheet



#	POB (KLD)	Gest	Gender	BW	Apgar1< 6	Apgar5< 6	HIVe	Anaemia	MA	PDA	Inotropes	RD	High HGT	Low HGT	Low temp	HMD	NEC	PH	IVH	NNE	Sepsis	cong	Io Steroid	HPT	DM	PET	Cardiac	HIV	PPROM	CI	Infection	APH	IUGR	Demised
1	1	30	0	1450	1	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
2	1	30	1	1400	0	0	1	0	0	0	1	0	0	0	0	1	1	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	0
3	1	30	0	1170	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
4	1	29	1	1200	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0
5	1	29	1	1020	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0
6	1	29	0	1200	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	30	1	1890	1	1	0	1	1	0	0	0	0	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	1	0	0	0	0	0
8	1	27	0	1300	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	1	0	0	0
9	0	29	0	900	0	0	1	0	0	1	0	0	0	0	0	1	1	0	0	0	1	0	1	0	0	0	0	1	1	0	0	0	0	0
10	1	28	1	1490	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	1	0	1	0	0	0	0	0	1	0	0	0	0	0
11	1	30	1	1300	0	0	1	0	0	1	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0
12	1	27	1	900	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0
13	0	30	1	1150	1	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1	1	0	0	0	0	0
14	1	30	0	1300	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	1	1	0	1	0	1	1	0	0	0	0	0
15	1	28	1	980	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0
16	0	29	0	1200	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
17	1	30	1	1200	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	29	0	1120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
19	1	28	0	1190	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	1	31	1	1490	1	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
21	0	28	0	1100	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	1	0
22	1	31	1	1400	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	1	0
23	0	33	0	1400	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
24	1	31	1	1300	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
25	1	28	1	1300	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
26	1	31	1	1480	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0
27	1	28	1	1200	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0
28	1	30	1	1400	1	1	1	1	1	0	0	0	0	1	0	1	1	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0
29	1	33	0	1400	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	1	28	0	900	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
31	1	31	0	1100	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0
32	0	31	1	1480	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0



Modifiable factors									
Final cause of neonatal death_1	Final cause of neonatal death_2	Final cause of neonatal death_3	Primary obstetric cause of death_1	Maternal obstetric condition	Patient associated_1	Patient associated_2	Administrative_1	Medical personel associated_1	Medical personel associated_2
0299 Other cpmplications of hypoxia									
0299 Other cpmplications of hypoxia									
0105 IVH	0102 HMD	0201 HIE	0999 Other maternal disease	0801 Chronic hypertension			0216 Personnel not sufficiently trained to manage the patient	0332 Neonatal resuscitation inadequate	
0101 Extreme multi-organ immaturity									

Appendix E PIPP codes

Causes of Death

0101 Extreme multi-organ immaturity
0102 HMD
0103 NEC
0104 Pulmonary haemorrhage
0105 IVH
0199 Other immaturity related cauese
0201 HIE
0202 Meconium Aspiration
0203 Persistent fetal circulation
0299 Other cpmplications of hypoxia
0301 Septicaemia
0302 Pneuminia
0303 Congenital syphillis
0304 HIV infection
0305 Congenital infection
0306 Group B Streptococcal infection
0307 Meningitis
0308 Nosocomial infection
0309 Tetanus
0399 Other infection
0401 CNS abnormalities
0402 CVS abnormalities
0403 Renal abnormalties
0404 Chromosomal abnormalities
0406 Biochemical abnormality
0407 Respiratory abnormalities
0501 Subaponeurotic haremorrhage
0599 Other trauma
0601 Isoimmunisation
0602 Non immune hydrops
0603 SIDS
0604 Apneoic attacks in 1st week
0605 Haemorrrhagic disease of new born
0606 Aspiration pneumonia
0607 Hypovoleamic shock
0608 Hypothermia
0609 Hypoglycaemia
0699 Other
0701 Unknown
0901 Intrauterine

Maternal Obstetric cause

0101 Healthy mom
0201 MVA
0202 Other accidents
0203 Assault
0204 Rape
0205 herbal medicine
0299 Other coincidental condition
0301 Cardiac disease
0302 Endocrine disease
0303 GIT disease
0304 CNS disease
0305 Respiratory disease
0306 Haematological disease
0307 Genitourinary disease
0308 Autoimmune disease
0309 Skeletal disease
0310 Psychiatric disease
0311 Neoplastic disease
0399 Other Medical and surgical disorders
0401 PCP
0402 Other pneumonia
0403 TB
0404 Endocarditis
0405 UTI
0406 Appendicitis
0407 Malaria
0408 Cryptococcal meningitis
0409 Other meningitis
0410 Kaposi sarcoma
0411 Toxoplasmosis
0412 Cholera
0413 Hepatitis
0414 Gastroenteritis
0415 Wasting syndrome
0416 complication of ARVs
0499 Other non pregnancy related infections
0501 Extrauterine pregnancy
0601 Chorioamnionitis with ruptured uterus
0602 Chorioaminionitis with intact membranes
0701 Abruption with hypertension
0702 Abruption without hypertension
0703 Placenta previa
0704 Other APH not specified
0705 Ruptured uterus with previous c/s
0706 Ruptured uterus without previous c/s
0801 Chronic hypertension
0802 Proteinuric hypertension
0803 Eclampsia
0804 HELLP
0805 Liver rupture
0806 Acute fatty liver
0807 Pregnancy induced hypertension without protenuria
0901 Complications of general anaesthesia
0902 Complication of epidural aneasthesia
0903 Complications of spinal anaesthesia
1001 Pulmonary embolism
1002 Amniotic fluid embolism
1101 Acute collapse - cause unknown

Avoidable factors patient associated

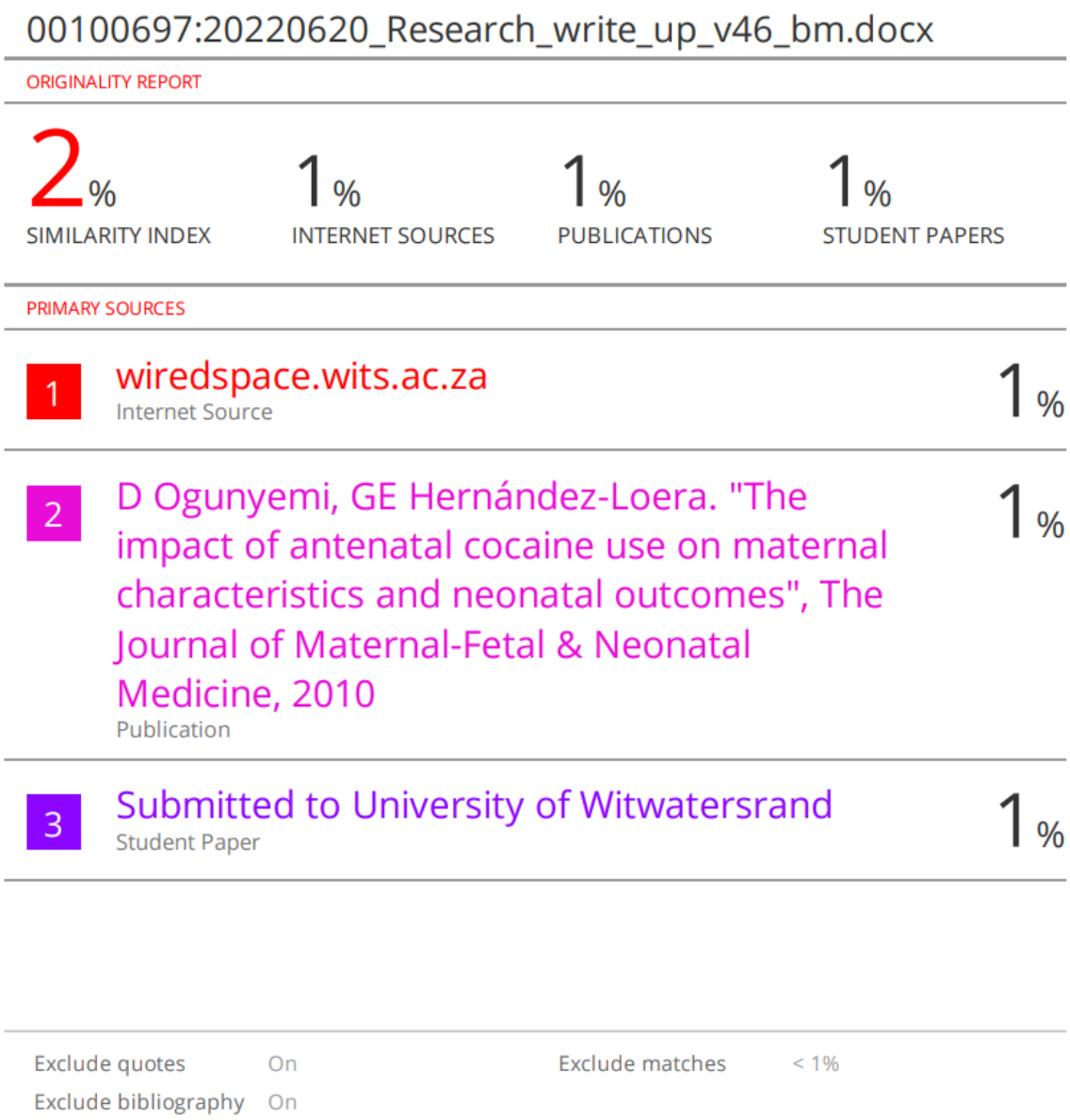
0101 Never initiated antenatal care

0102 Booked late in pregnancy
0103 Infrequent visits to antenatal clinic
0104 Failed to return on the prescribed date
0105 Inappropriate response to rupture of membranes
0106 Inappropriate response to antepartum haemorrhage
0107 Inappropriate response to poor fetal movements
0108 Delay in seeking medical attention during labour
0109 Delay in seeking help when baby ill
0110 Declines admission/treatment for personal/social rea
0111 Partner/Family declines admission/treatment
0112 Alcohol abuse
0113 Smoking
0114 Illegal drug use
0115 Assault
0116 Attempted termination of pregnancy
0117 Infanticide
0118 Abandoned baby
0199 Other patient associated factors

Avoidable factors Administrative
0201 Lack of transport - Home to institution
0202 Lack of transport - Institution to institution
0203 Lack of adequate neonatal transport
0204 No syphilis screening performed at hospital / clinic
0205 Result of syphilis screening not returned to hospital/clinic
0206 No on-site syphilis testing available
0207 No Motherhood card issued
0208 No dedicated high risk clinic at referral hospital
0209 Inadequate facilities/equipment in neonatal unit/nur
0210 Inadequate theatre facilities
0211 No accessible neonatal ICU bed with ventilator
0212 Inadequate resuscitation equipment
0213 Insufficient blood / blood products available
0214 Insufficient nurses on duty to manage the patient ade
0215 Insufficient doctors available to manage the patient
0216 Personnel not sufficiently trained to manage the pati
0217 Personnel too junior to manage the patient
0218 Staff rotation too rapid
0219 Anaesthetic delay
0220 Theatre delay: staff not available
0221 Theatre delay: all theatres occupied
0222 Congenital abnormality not diagnosed: No ultrasound available
0299 Other administrative problems (power outages)

Avoidable factors Medical associated
0301 No response to history of stillbirths, abruptio etc.
0302 No response to maternal glycosuria
0303 No response to poor uterine fundal growth
0304 No response to maternal hypertension
0305 No response to positive syphilis serology test
0306 No response to apparent postterm pregnancy
0307 No response to history of poor fetal movement
0308 No antenatal response to abnormal fetal lie
0309 Multiple pregnancy not diagnosed antenatally
0310 Physical examination of patient at clinic incomplete
0311 GP did not give card/letter about antenatal care
0312 Medical personnel overestimated fetal size
0313 Medical personnel underestimated fetal size
0314 Fetal distress not detected antepartum; fetus monitored
0315 Fetal distress not detected antepartum; fetus not monitored
0316 Antenatal steroids not given
0317 Poor progress in labour, but partogram not used
0318 Poor progress in labour, but partogram not used correctly
0319 Poor progress in labour - partogram interpreted incorrectly
0320 Fetal distress not detected intrapartum; fetus monitored
0321 Fetal distress not detected intrapartum; fetus not monitored
0322 Breech presentation not diagnosed until late in labour
0323 Multiple pregnancy not diagnosed intrapartum
0324 Incorrect management of hypertensive disease
0325 Incorrect management of antepartum haemorrhage
0326 Incorrect management of premature labour
0327 Incorrect management of cord prolapse
0328 Iatrogenic delivery for no real reason
0329 Management of 2nd stage: prolonged with no intervention
0330 Management of 2nd stage: inappropriate use of forceps
0331 Management of 2nd stage: inappropriate use of vacuum
0332 Neonatal resuscitation inadequate
0333 Neonatal care: inadequate monitoring
0334 Neonatal care: management plan inadequate
0335 Baby managed incorrectly at Hospital/Clinic
0336 Baby sent home inappropriately
0337 Delay in doctor responding to call
0338 Doctor did not respond to call
0339 Delay in medical personnel calling for expert assistance
0340 Delay in referring patient for secondary/tertiary treatment
0341 Nosocomial infection
0342 Inadequate / No advice given to mother
0343 Congenital abnormality not diagnosed; U/S examination not performed
0344 Congenital abnormality not diagnosed; U/S examination was performed
0399 Other medical personnel associated factors (excessive bagging)
0401 Insufficient notes
0402 File missing
0403 Antenatal card lost

Appendix F Turnitin report



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ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	wiredspace.wits.ac.za Internet Source	1%
2	D Ogunyemi, GE Hernández-Loera. "The impact of antenatal cocaine use on maternal characteristics and neonatal outcomes", The Journal of Maternal-Fetal & Neonatal Medicine, 2010 Publication	1%
3	Submitted to University of Witwatersrand Student Paper	1%

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Appendix G Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Nalishebo Mothibatsela (Student number: 0702307F) am a student registered for the degree of MMed in the academic year 3.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 11/10/2022

Appendix H Author guidelines SAJCH

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 arenot.

- 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 3 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.

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.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather: Each row of data must have its own proper row.

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

Rather: Combine into one column, *n* (%).

Do not: have overlapping categories, e.g.

Rather: Use <> symbols or numbers that don’t overlap.

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Q2qa Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x