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Title Page

Mortality risk factors of Very Low Birth Weight infants at a tertiary hospital in the Eastern Cape, South Africa.

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Prospective cohort study of mortality risk factors of VLBW infants in the Eastern Cape, South Africa.

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Dr Isabel Michaelis contribution consisted of funding acquisition, study design, investigation, data curation, supervision and drafting the initial manuscript.

Dr Ncomeka Mayisane contributed to study design, investigation, data curation and reviewing the manuscript.

Prof Ingeborg Krägeloh-Mann contribution consisted of supervision and writing and reviewing the final manuscript.

Mrs Mikateko Mazinu contribution consisted of data curation and data analysis.

Mrs Esme Jordaan contribution consisted of data curation and data analysis.

What is known about this topic?

Neonatal mortality rate in South Africa is 32 % of the under five- year mortality rate.

Preterm and very low birth weight babies are most affected.

Studies about neonatal mortality have been done in the main cities in South Africa.

What does this study add?

To our knowledge this is the first prospective study about the mortality rate and mortality risk factors of VLBW infants in the Eastern Cape of South Africa.

It shows that the chance of survival for those babies is lower than in other urban settings.

Equipment, facilities, skills and staffing should be improved in those settings.

Background:

Neonatal mortality is worldwide a major contributor to the number of deaths in children under 5 years of age. The primary objective of this study was to assess the overall mortality rate of babies with a birth weight of less than 1501 g in a neonatal unit at a tertiary hospital in the Eastern Cape Province, South Africa. Furthermore, different maternal and offspring related risk factors for mortality were analysed.

Methods:

This is a prospective cohort study which included babies admitted to the neonatal wards of the hospital within their first 24 hours of life and with a birth weight below 1501 g.

Results:

173 infants were admitted to the neonatal department with a birth weight below 1501g. The overall survival rate to hospital discharge was 68%. Only 46.5% of babies born with a birth weight below 1001 g survived their hospital stay.

Main predictors for survival were higher gestational age and higher birth weight. Need for ventilator support and sepsis increased mortality risk significantly, as did maternal factors such as HIV infection or teenage age. Babies born to a mother with gestational hypertension had a two-fold increased chance of survival.

Conclusion:

This is the first prospective study looking at survival of very low birth weight babies in the underprivileged part of the Eastern Cape of South Africa. Compared to better resourced public hospitals in the country the survival rate remains unacceptably low. More needs to be done to prevent preterm and low birth weight births; the facilities caring for these most vulnerable persons must be equipped and staffed accordingly.

Introduction:

Despite improved survival rates of neonates worldwide, the survival of preterm and low birth weight babies is still challenging, especially in middle and low-income countries (1–4).

In 2018 the WHO described a worldwide increase of babies born prematurely over the last two decades. The incidence has been estimated between 5–18% (5,6). The rate of babies born with a very low birth weight (VLBW) varied between different countries, for example it has been found to be 3% in South Africa, while in the USA it is between 1.23 and 1.43% (7–9). Furthermore, prematurity and low birth weight have been identified as the leading causes of mortality in children less than five years of age (5,10–12). It is also well known that neonatal mortality varies considerably amongst high and low-middle income countries for example, a mortality rate of 15% in the United States, while India reports 24.6% for VLBW infants (13,14).

In South Africa, neonatal mortality accounted for 32% of the under-5 mortality rate (4,15,16). Kalimba and Ballot (17) studied the survival rate of extremely low birth weight (ELBW) babies (babies weighing less than 1000g at birth) born between 2006 and 2010 in Johannesburg and found that only 25.6% of babies born with a birth weight of less than 900g survived their hospital stay, with birth weight and gestational age being the strongest predictors for survival. A newer retrospective cross sectional South African study found an overall survival rate in VLBW babies (500g–1499 g) of 75.7% (18).

However, there are other known contributory factors, which can be divided into offspring or maternal related risk factors. Examples of baby related risk factors studied in the literature are low Apgar scores, respiratory distress syndrome, intubation and mechanical ventilation, sepsis and hemodynamic instability (Terzic and Heljic, 2012; Kabilan and Kumar, 2018). Maternal or obstetric risk factors include eclampsia, alcohol consumption, smoking, low socioeconomic status, scarce antenatal care and human immunodeficiency virus (HIV) infection (17,21–23). Several studies suggest an increased risk for premature labour in mothers taking antiretroviral treatment for HIV infection during pregnancy (24–27), while others did not find a relationship (28). This is of note, as 30.8% of pregnant women in South Africa in 2015 tested positive for HIV infection, and are put on treatment as soon as the infection is diagnosed (Department of Health Republic of South Africa, 2017).

Setting:

Frere Hospital is a public tertiary hospital in East London in the Eastern Cape Province in South Africa, with a seven bed paediatric intensive care unit (PICU), which cares for neonates, paediatric medical and surgical patients. Because of this very limited PICU access, babies with a weight below 1000 g are not provided with invasive ventilatory support. These babies will receive surfactant if needed and continuous positive airway pressure (CPAP) ventilation is available for six infants in the high care neonatal unit. Stable neonates with a weight >1000 g are referred to the general nursery ward, where they receive kangaroo care (KMC) in the ward and, if necessary, intravenous fluids and/or antibiotics and oxygen. Once clinically stable, off oxygen support, tolerating full enteral feeds and weighing more than 1500 g, infants will be transferred to the KMC ward until mothers are competent in caring for their baby and the weight has increased to at least 1700 g.

Frere Hospital is the tertiary neonatal and obstetric referral centre for obstetric units and for surrounding district hospitals in the remote part of the Eastern Cape Province. These areas were deprived from adequate infrastructure during the Apartheid regime and are still one of most underprivileged parts of South Africa.

Materials and Methods:

This was a prospective cohort study. All babies born at, or admitted within the first 24 hours of life into the neonatal unit with a birth weight equal or below 1500 g and without any life-threatening malformations were included (n=173). The recruitment period lasted from December 2017 to November 2018. During this period 4207 babies were born at Frere Hospital obstetric department.

After obtaining the approval of the institutional ethics committee (086/2017) and after receiving written consent from the mother of the baby, data concerning mother and child during the pre-, peri- and neonatal period were collected from the maternal and neonatal case sheets, as well as from a questionnaire filled in with the mother (available as supplements). The babies were followed up until discharge or death. All babies received standard care during this period, as outlined above.

Patient and Public Involvement:

Infants born with a very low birth weight are followed up in a high risk clinic and often have to be referred to a neurodevelopmental clinic for assessment. During these follow-up

appointments the necessity for the check-ups is often questioned and if pathologies are found the possible causes for those lye mostly in the perinatal and admission history. Being able to answer those questions for our setting a study involving the postnatal admission stay needed to be scrutinized. The patients, being mother-newborns pair, were not involved in the study design. While doing the study and recruiting every new-born being admitted in our wards with a birth weight below or equal to 1500g was assessed for inclusion in our study, no recruitment from there side was necessary.

The results of this study will be verbally communicated to the mothers during the follow-up appointments.

Statistical analysis:

Demographic data is presented as frequencies (percentages) for categorical data, and as means (SD) for numerical data. To test for association between the outcome variable (mortality) and the predictor variables, a log binomial regression model was used. Multiple regression analysis was performed for all significant variable from the baby and mother's univariate analysis separately. A stepwise regression was used to exclude non-significant variables one at a time. The standard for significance for all analyses was $p<0.05$. Data were analysed using STATA version 15.

Offspring and Maternal multiple regression analysis:

These analyses include all variables with p value ≤ 0.1 from the baby univariate analysis table. All variables with small cell number (n≤6) were excluded from the multiple regression model. Apgar at 5 minutes was also excluded in the analysis due to colinear relationship between Apgar 1 and Apgar 5.

Results:

One hundred and sixty-one VLBW infants were recruited during the study period, of those 45 (28.0%) died before discharge and 116 (72.0%) were discharged home. All 116 babies discharged home from Frere Hospital received a follow up date for the high-risk clinic (Figure 1).

Demographics:

Of the 161 babies included in the study, 96 were female (59.7%) and 65 were male (40.3%). The mean birth weight was 1156 g (580 g – 1 500 g) with SD of 233 g. Almost three quarters (73.4%) of the babies had a birth weight above 1000 g. The mean gestational age in weeks

was 32.2 with SD of 2.6 weeks. About half were born at the gestational age of 26–32 weeks (n=78; 49.1%). Most babies were delivered by normal vaginal delivery (n=97; 60.3%), to a mother who was unemployed (n=135; 84.9%). More than a third of the babies (n=58; 36.0%) were HIV exposed during pregnancy and birth. Almost all HIV exposed babies tested negative for HIV infection at birth with a negative birth HIV-polymerase chain reaction (HIV-PCR) (n=55; 94.8%). Three babies, who died a few hours after birth, did not receive an HIV-PCR at birth and their status is therefore unknown. 146 (91.8%) of the babies were exclusively breastfed, nine were exclusively formula fed and four received mixed feeding.

The maternal age ranged between 14 and 46 years, with a mean maternal age of 27 years (SD = 6.7). Eighteen percent of the mothers were teenagers (n=30). Only 13 (8.2%) of the mothers were married, 78 (48.5%) were in a stable relationship and 67 (41.6%) mothers were single. For 3 (1.9%) mothers, no such information was available. Less than half (45.6%) of the mothers attended no or primary school only, while 54.4% went through secondary or tertiary education. Almost 90% (89.9%) of the mothers lived in a house which had electricity, but only 62.3% had running water on their property. Fifty-eight (36.0%) mothers had HIV infection diagnosed before, during pregnancy, or at birth. Thirty-nine of them (67.2%) had been on antiretroviral (ARV) treatment at delivery for more than 4 weeks. Sixteen (27.6%) mothers had been on ARV treatment for less than 4 weeks or were not on treatment at all when giving birth, and their babies were thus considered at high risk for HIV transmission and treated accordingly.

The in-hospital survival rate for all babies born with a birth weight below 1500 g and admitted to our neonatal wards was 118/173 (68.2%), and for the babies included in our study the survival rate was 116/161 (72.0%).

Risk factors for in hospital mortality:

Neonatal related risk factors:

Univariate regression analysis was used to examine the association between the outcome death and individual risk factors. The significant risk factors were low gestational age ($p<0.0001$; RR=4.2; 95% CI: 2.9–5.9), the need for resuscitation at birth ($p< 0.0001$; RR=4.5; 95% CI: 3.4–5.8) or during hospital stay ($p=0.011$; RR=12; 95% CI: 5.8–25.9), low 1 and/or 5 minute Apgar score ($p\leq0.0001$; RR=2.5; 95% CI: 2.0–3.1 and $p<0.0001$; RR=2.4; 95% CI: 2.1–2.8), and sepsis ($p<0.0001$; RR=6.4; 95% CI: 3.8–10.9) were significantly associated with death (table 1). Male gender was not associated with higher mortality risk ($p=0.935$; RR=1.0; 95% CI: 0.7–1.5) (table 1).

Table 1: Univariate analysis of risk factors associated with mortality in VLBW infants

Description	category	n*	%*	n died**	%died**	SE	P	RR	95%CI	
GA (weeks)	25-32 wks	78	49,06	36	46,2	3,28				
	33-37 wks	81	50,94	9	11,1	1,64	0,000	4,2	2,93	5,88
HIV exposed	no (0)	103	63,98	31	30,1	2,11		1,2	1,00	1,56
	yes (1)	58	36,02	14	24,1	2,42	0,053			
birth weight	>1000g (0)	118	73,29	22	18,6	2,31		2,9	2,08	3,96
	<=1000g (1)	43	26,71	23	53,5	3,73	0,000			
Resuscitation at birth	no (0)	89	55,97	10	11,2	1,53				
	yes (1)	70	44,03	35	50	2,09	0,000	4,5	3,43	5,78
Apgar 1 min	7-10 (=0)	110	68,32	21	19,1	1,77				
	0-6 (=1)	51	31,68	24	47,1	2,23	0,000	2,5	1,99	3,05
Apgar 5 min.	7-10(=0)	144	89,44	35	24,3	1,66				
	0-6(=1)	17	10,56	10	58,8		0,000	2,4	2,12	2,77
HMD	no (0)	85	52,8	16	18,8	1,50				
	yes (1)	76	47,2	29	38,2	3,03	0,000	2,0	1,72	2,38
Other	no (0)	131	81,37	33	25,2	1,73				
	yes (1)	30	18,63	12	40	5,07	0,001	1,6	1,20	2,09
Oxygen support	no (0)	50	31,06	2	4	0,63				
	yes (1)	111	68,94	43	38,7	2,42	0,000	9,7	7,39	12,68
Surfactant given	no (0)	107	66,46	16	15	1,80				
	yes (1)	54	33,54	29	53,7	2,49	0,000	3,6	2,77	4,65
Weight gain	no	85	64,89	6	7,1	1,12				
	yes	46	35,11	11	23,9	3,60	0,000	3,4	2,21	5,19
Sepsis	no (0)	69	46,94	4	5,8	1,21				
	yes (1)	78	53,06	29	37,2	3,17	0,000	6,4	3,78	10,88
ICH	no (0)	120	88,24	13	10,8	1,33				
	yes (1)	16	11,76	9	56,3	9,83	0,000	5,2	3,03	8,90
PDA	no (0)	104	77,04	19	18,3	2,06	0,002	2,8	1,47	5,47
	yes (1)	31	22,96	2	6,5	1,67				
Resuscitation during admission	no (0)	112	74,17	7	6,3	2,45				
	yes (1)	39	25,83	30	76,9	2,12	0,011	12,3	5,85	25,88
Gender	male (0)	65	40,37	18	27,7	3,74				
	female (1)	96	59,63	27	28,1	2.59	0,935	1,0	0,7	1,5
Born before arrival	no (0)	150	93,17	43	28,7	1,77				
	yes (1)	11	6,83	2	18,2	7,36	0,278	0,6	0,28	1,45
Mom not been to ANC	no (0)	136	84,47	37	27,2	1,97				
	yes (1)	25	15,53	8	32	3,40	0,218	1,2	0,91	1,52

*The number and percentage per risk factor category
**The number and percentage of babies who died per risk factor category
SE standard error from the model

RR relative risk with 95% confidence interval
GA: gestational age, HIV: human immunodeficiency virus, HMD: hyaline membrane disease, ICH: intracranial haemorrhage, PDA: persistent ductus arteriosus, ANC: antenatal clinic.

Maternal risk factors for the univariate model:

The risk of dying while still in hospital was higher in babies of teenage mothers (p=0.004; RR=1.2; 95% CI: 1.1–1.5) and if there was no refrigerator in the house the mother lived in (p=0.038; RR=1,2: CI: 1.01–1.48). Maternal hypertension (RR=0,6; 95% CI: 0.5–0.8; p=0.0001) and preeclampsia (RR=0,7: 95% CI: 0.6–0.8; p=0.0001) significantly decreased the mortality risk in the babies. Education level of the mother and other socio-economic status factors were not related to a higher mortality risk during admission in our study (table 2).

Table 2. The univariate associations between mortality and maternal related risk factors.

Description	Codes	n	%	n died	%died	P	RR	95%CI	
Age of mother (years)	<=20yrs	30	18,63	10	33,3	0,004	1,2	1,07	1,45
	>20yrs	131	81,37	35	26,7				
Marital status	marr /stale rel	13	16,25	3	23,1				
	no partner	67	83,75	18	26,9	0,574	1,2	0,69	1,98
Substance abuse	no(0)	147	91,88	40	27,2				
	yes(1)	13	8,13	4	30,8	0,761	1,1	0,51	2,50
Hypertension	no(0)	91	57,96	29	31,9				
	yes(1)	66	42,04	13	19,7	0,000	0,6	0,49	0,77
PROM	no(0)	134	85,35	35	26,1				
	yes(1)	23	14,65	7	30,4	0,602	1,2	0,66	2,07
Pre-eclampsia	no(0)	117	74,52	34	29,1				
	yes(1)	40	25,48	8	20	0,00	0,7	0,57	0,82
Other illnesses	no(0)	125	79,11	31	24,8				
	yes(1)	33	20,89	11	33,3	0,023	1,3	1,04	1,74
Medication	no(0)	130	81,25	40	30,8				
	yes(1)	30	18,75	4	13,3	0,004	0,4	0,25	0,77
Employment	no(0)	135	84,91	39	28,9				
	yes(1)	24	15,09	5	20,8	0,055	0,7	0,52	1,01
Electricity	no(0)	16	10,06	3	18,8				
	yes(1)	143	89,94	41	28,7	0,151	1,5	0,86	2,73
Running water	no(0)	60	37,74	16	26,7				
	yes(1)	99	62,26	28	28,3	0,640	1,1	0,83	1,36
Refrigerator	no(0)	50	31,45	12	24				
	yes(1)	109	68,55	32	29,4	0,038	1,2	1,01	1,48
Education	Primary	72	45,57	22	30,6	0,119	1,3	0,94	1,66
	secondary/tert	86	54,43	21	24,4				
RVD infected	no(0)	101	63,52	30	29,7				
	yes(1)	58	36,48	14	24,1	0,075	0,8	0,65	1,02
ARTs	FTC	45	93,75	10	22,2				
	second line	2	4,17	0	0				

	Other	1	2,08	0	0				

PROM: premature rupture of membranes, RVD: retroviral disease, ARTs: anti-retroviral treatment

Offspring and maternal multiple regression analysis:

Significant independent statistical associations for many offspring-related variables could be seen: Gestational age and birth weight with p<0.001: RR=1; 95% CI: 0.95–0.95 and p=0.004: RR=1.2; 95% CI: 1.05–1.32 respectively. Exposure to an HIV-infected mother became significant: p<0.001: RR=2; 95% CI: 1.76–2.21. Resuscitation at birth (p<0.001; RR=2.9; 95% CI: 2.25–3.69), HMD (p<0.001; RR=0.93; 95% CI: 0.93–0.93) and the following necessity to give surfactant (p<0.001; RR=1.65; 95% CI:1.47–1.84) correlated with an increased mortality risk. ICH was also found to be a significant risk factor for in-hospital mortality with p<0.001; RR=2.01; 95% CI: 1.80–2.26. Unsurprisingly the need for resuscitation during hospital stay correlated with an increased risk of dying (p=0.011; RR=13.7; 95% CI: 7.17–26.19).

The multiple regression analysis of maternal risks showed, that being born to a mother with hypertension was protective and decreased the risk of dying in hospital (p<0,001; RR=0.6; 95% CI: 0.51–0.77). The risk of mortality was 37% lower for the babies born to mothers with hypertension compared to mothers without. All other maternal factors were non-significant in the multivariate analysis.

Discussion:

The incidence of VLBW in our hospital was 41 in 1000 births for the year from December 2017 to November 2018 (95%CI: 35.0–47.7). The prevalence of VLBW in our hospital was 4,7%. This is a high prevalence of VLBW babies born compared to developed countries, such as the USA with a prevalence of 1,4% (30), Europe between 0,8–1,2 (31) and China with 1,9% (32) but also compared to the prevalence found in Soweto, South Africa of 3% and in Brazil of 0,9%–3% (1,7,33). However, it is within the prevalence of 3–7% reported worldwide (3,13).

Survival of infants below 1000 g birth weight was 46.5% compared to 81.4% for those weighing between 1000 g and below 1500 g at birth. The overall neonatal survival rates of VLBW compare well with some other developing and developed countries in the last 15 years, with 63.1% in India (2), 70.9% in Iran (3), and 71.8% in South Korea (11) or 68% in the Eastern Mediterranean Region (34). It is, though, lower than in other parts of South

Africa where the survival rate was reported as 73.4%, 75% and 75.7% respectively (18,35,36) and much lower than in most developed countries, where the survival rate was found to be between 86.6% and 90.3% (12,23,31,32,37–42). This shows, that the Eastern Cape Province lags behind other South African urban settings in the effort to improve the survival of VLBW neonates.

Consistent with other studies examining the causes of mortality in VLBW babies, birth weight (specifically extremely low birth weight) and low gestational age were found to be major predictors for neonatal mortality in our study population (17,20,23,31,35,43,44). Complications of prematurity, such as the development of hyaline membrane disease and the associated need for surfactant application was associated with a significant increased risk of mortality.

Interestingly our study could not confirm the wide range of maternal factors increasing the risk of death during admission found in other studies such as no antenatal care, premature rupture of membranes, maternal primi-parity, mode or complication of delivery (17,21,22,27,44,45). The only socio-economic factor showing in the univariate analysis as a significant higher risk of baby dying during admission was when the mother was of teenage age, and whether a refrigerator was present in the household the mother lived in. These factors lost significance, however, when a multivariate analysis was used. Here exposure to an HIV-infected mother became significant.

Infants born to mothers with hypertension had a better chance of survival than those born to a mother who did not had hypertension. A multicentre prospective cohort study from Brazil by de Alemida *et al*. found the same correlation (1).

Although a substantial percentage (36%) of the babies were born to HIV infected mothers, all but three (who all died before HIV-PCR could be taken) were born with a negative HIV-PCR infection. However, 17.2% (n=10) of the HIV infected mothers still had not received any ART before giving birth. However, all mothers received prophylaxis in labour and their babies were treated with nevirapine and zidovudine as high risk infants.

Conclusion:

Our study shows that the survival rate in VLBW babies is comparable to other developing countries worldwide, but lower than in the urban hospitals of South Africa. Similar to the findings of many other studies, gestational age and birth weight were the main baby-related

predictors for survival, and HIV infection of the mother was the only maternal risk factor, while pregnancy hypertension was found to be protective.

These findings indicate that the survival of VLBW and especially for ELBW babies are lower in a setting with low resources. The Eastern Cape Province is known to be one of the most disadvantaged areas in South Africa and this still has an impact on the survival of the most vulnerable members of our society.

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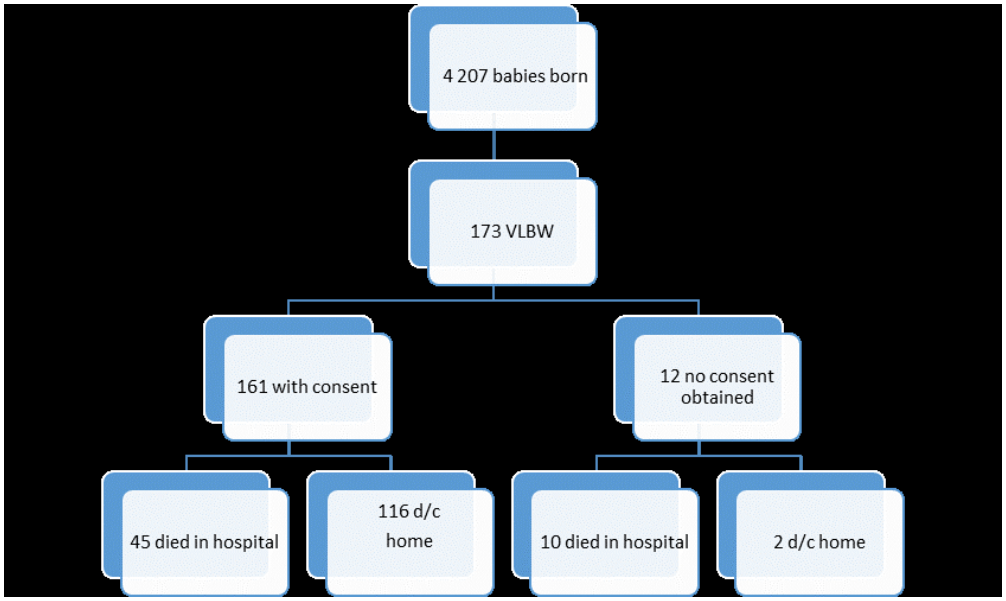
4 207 babies born
173 VLBW
161 with consent
12 no consent obtained
45 died in hospital
116 d/c home
10 died in hospital
2 d/c home

FNo:

Data of child at birth:

Date of birth:	□		
Gender	□ female	□ male	
Gestational age:	□		
Mode of delivery:	□ NVD	□ Sectio	□ Vacuum or forceps
HIV exposed:	□ exposed	□ unexposed	
PMTCT	□ yes	□ no	
Birth weight:	gr		
Length:	cm		
Head circumferences:	cm		
Resuscitation at birth:	□ yes	□ no	
APGAR	1min	5 min	10 min
Diagnosis at birth:			
Oxygen support	□ yes	□ no	
Surfactant:	□ yes	□ no	
Ventilatory support:	□ none	□ CPAP	□ Invasive ventilation
If yes, how long	days		
Maximum of oxygen needed:	□ < 60%	□ > 60%	
Feeding option	□ Breast	□ formula	□ mixed
Trend of weight gain:	□ normal	□ abnormal	
Sepsis :	□ yes	□ no	
PVL or IVH:	□ yes	□ no	
PDA:	□ yes	□ no	
Steroid use (postnatal):	□ yes	□ no	
Resuscitation during hospital stay:	□ yes	□ no	

Mother's Data:

Age of mother:

Number of pregnancy: □

Children alive: □

Marital status: □ married □ stable relationship □ single

During pregnancy:

Hypertension: □ yes □ no

PT rupture of membranes: □ yes □ no

Preeclampsia/ Eclampsia □ yes □ no

Any other problems (e.g. seizures, drug abuse, diabetes)

SES of mother: □ employed □ unemployed

Electricity at home: □ yes □ no

Running water at home: □ yes □ no

Fridge: □ yes □ no

Educational level: □ primary school □ matric □ tertiary education

Mother's HIV status: □ positive □ negative

If positive:

ARVs since when: weeks before birth

ARVS: □ FDC □ second line □ other

Disclosure to anyone:

Has partner been tested:

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Title Page

Prospective cohort study of mortality in very low birth weight infants in a single centre in the Eastern Cape Province, South Africa

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I hereby confirm that neither the submitted paper nor any parts of it have been published or submitted anywhere else.

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Dr Isabel Michaelis' contribution consisted of funding acquisition, study design, investigation, data curation, supervision and drafting the initial manuscript.

Dr Ncomeka Mayisane contributed to study design, investigation, data curation and reviewing the manuscript.

Prof Ingeborg Krägeloh-Mann contributed to supervision, writing and reviewing the final manuscript.

Mrs Mikateko Mazinu contributed to data curation and data analysis.

Mrs Esme Jordaan contributes to data curation and data analysis and writing and reviewing the final manuscript.

What is known about this topic?

The perinatal mortality rate in sub-Saharan Africa is about 30 per 1000 live births. Preterm and VLBW infants account for a large number of neonatal deaths. Although South Africa is considered an upper-middle-income country by the World Bank, survival of VLBW varies greatly dependent on resources. Survival of VLBW infants in studies from South Africa are about 75%.

What does this study add?

Survival of VLBW infants was 68% in our cohort. This shows that the chance of survival for those babies in our setting is lower than in other South African urban settings. Causes for this difference should be further explored.

Background:

Neonatal mortality is a major contributor worldwide to the number of deaths in children under 5 years of age. The primary objective of this study was to assess the overall mortality rate of babies with a birth weight of less than 1500g in a neonatal unit at a tertiary hospital in the Eastern Cape Province, South Africa. Furthermore, different maternal and infant related factors for higher mortality were analysed.

Methods:

This is a prospective cohort study which included infants admitted to the neonatal wards of the hospital within their first 24 hours of life and with a birth weight equal to or below 1500g.

Results:

173 very low birth weight (VLBW) infants were admitted to the neonatal department between November 2017 and December 2018. The overall mortality was 32%. More than half (53.5%) of the infants with a birth weight below 1000g died during admission.

Main predictors for mortality were lower gestational age and lower birth weight. Need for ventilator support and sepsis increased mortality risk significantly, as did maternal factors such as HIV infection and age below 20 years. VLBW babies born to a mother with gestational hypertension had a two-fold increased chance of survival, most likely due to associated intrauterine growth restriction with higher gestational age at birth relative to weight.

Conclusion:

This prospective study looked at survival of very low birth weight babies in an underprivileged part of the Eastern Cape of South Africa. Compared to other public urban hospitals in the country the survival rate remains unacceptably low. Further research is required to find the associated causes and appropriate ways to address these.

Introduction:

Despite improved survival rates of neonates worldwide, the survival of preterm and low birth weight babies is still a challenge, especially in middle- and low-income countries (1–4).

In 2018, the World Health Organisation (WHO) described a worldwide increase of babies born prematurely over the last two decades. The incidence has been estimated between 5 to 18% of all life births (5,6). The prevalence of babies born with a very low birth weight (VLBW) varies between different countries. For example, in one South African study the prevalence was 3%, while in the USA it lies between 1.23 and 1.43% (7–9). Furthermore, prematurity and low birth weight have been identified as the leading causes of mortality in children less than five years of age (5,10–12). It is also well known that neonatal mortality for VLBW infants varies considerably amongst high- and low-middle income countries: a mortality rate of 15% is found in the United States (13), 20% by the Vermont Oxford network (14), 29.1% in Iran (3), 28.2% in South Korea (11), 32% in the Eastern Mediterranean Region (15), and 24.6% in India (16). Some single centres worldwide show a lower mortality rate with 9.5%, 12.4%, 13.0% and 17.2% in single centres in Singapore, Taiwan, Hong-Kong, Saudi-Arabia, respectively (14,17–19).

In South Africa, neonatal mortality accounted for 32% of the under-5 mortality rate (4,20,21). A recent study illustrated survival rates of VLBW neonates between different hospitals in the Western Cape Province of South Africa as characterized by unrestricted or restricted resources (22). The team found a significant difference with a survival rate of 84.4% and 70.4% respectively (22). Kalimba and Ballot (23) studied the survival rate of extremely low birth weight (ELBW) babies (babies weighing less than 1000g at birth) born between 2006 and 2010 in Johannesburg and found that only 25.6% of babies born with a birth weight of less than 900g survived their hospital stay, with birth weight and gestational age being the strongest predictors for survival. A newer retrospective cross-sectional South African study found an overall survival rate in VLBW babies (500g–1499g) of 75.7% (24).

However, there are also other known contributory factors, which can be divided into infant-or maternal-related risk factors. Examples of neonate-related risk factors studied in the literature include low Apgar scores, hyaline membrane disease (HMD), intubation and mechanical ventilation, sepsis, and hemodynamic instability (25,26). Maternal or obstetric risk factors include eclampsia, alcohol consumption, smoking, low socioeconomic status, scarce antenatal care and human immunodeficiency virus (HIV) infection (18,23,27,28). Several studies suggest an increased risk of premature labour in mothers taking antiretroviral treatment for HIV infection during pregnancy (29–32), while others did not find a

relationship (33). This is noteworthy, as 30.8% of pregnant women in South Africa tested positive for HIV in 2015, and are put on treatment as soon as the infection is diagnosed (34,35).

The primary aim of this study was to research neonatal mortality of VLBW infants admitted to the neonatal unit in a hospital in a mixed urban and rural setting in the Eastern Cape Province of South Africa. Secondly, the association between death and different maternal and neonatal factors were explored.

Setting:

Frere Hospital is a large (885 beds) public tertiary hospital in East London in the Eastern Cape Province in South Africa, with a seven-bed paediatric intensive care unit (PICU), which cares for neonates and paediatric medical and surgical patients. Because of this very limited PICU access, babies with a weight below 1000g are not provided with invasive ventilatory support due to poor survival. These babies will receive surfactant if needed and continuous positive airway pressure (CPAP) ventilation is available for six infants in the high care neonatal unit, which can cater for 12 infants altogether. This high care ward is constantly above capacity, often having to care for up to 20 infants, when there is only adequate space for the above-mentioned 12 neonates. Infants with a birth weight over 1000g will be taken to PICU and receive invasive ventilation if needed and if space is available for them. Stable neonates with a weight of more than 1000g are referred to the general nursery ward, where they receive kangaroo care (KMC) in the ward and, if necessary, intravenous fluids and/or antibiotics and oxygen. Once clinically stable, off oxygen support, tolerating full enteral feeds and weighing more than 1500g, infants will be transferred to the KMC ward until mothers are competent in caring for their baby and the weight has increased to at least 1700 g. Some stable babies might be transferred to their regional hospital once their weight has reached 1500g.

Frere Hospital is the tertiary neonatal and obstetric referral centre for obstetric units and for surrounding district hospitals in the middle part of the Eastern Cape Province. Some referrals centres are more than 300 km away. These areas were deprived of adequate infrastructure during the Apartheid regime and are still one of the most under-resourced and insufficiently managed parts of South Africa.

Materials and Methods:

This was a prospective cohort study. All babies born at the hospital, or admitted within the first 24 hours of life into the neonatal unit, with a birth weight equal or below 1500g and

without any life-threatening malformations were included. Neonates who were admitted to the neonatal ward or PICU beyond 24 hours of life were excluded as it was not possible to get sufficient information on those mother-infant pairs. Mothers were then approached for consent to include their data. The recruitment period lasted from December 2017 to November 2018.

The study was approved by the institutional ethics committee (086/2017) and, after receiving written consent from the mothers, data concerning mother and child during the pre-, peri- and neonatal period were collected from the maternal and neonatal case records, as well as from a questionnaire filled in with the mother (see supplements). The babies were followed up until discharge or death. All babies received standard care during this period, as outlined above.

Gestational age was determined by either an early ultrasound or by applying the Ballard gestational age scoring system. The different variables were defined as follows: a persistent ductus arteriosus as identified by echocardiogram; hyaline membrane disease by the presence respiratory distress; FiO_2 requirement above 40% followed by a confirmatory blood gas and typical X-ray signs; sepsis as clinical signs confirmed with a positive blood, urine or cerebrospinal fluid culture and/or raised C-reactive protein (CRP) taken at least 24 hours apart; normal weight gain was determined when weight loss after birth did not exceed more than 10% and birth weight was regained within 10-14 days of life; intracranial haemorrhage (ICH) was diagnosed with cranial ultrasound, which was only performed in clinically unstable infants with the clinical suspicion of ICH; resuscitation at birth included mask or invasive ventilation with or without cardiac compressions and medication.

Patient and Public Involvement:

Mothers of VLBW and preterm babies often spend weeks in the neonatal wards with their very small and often very sick infant. As such, this is already an extremely stressful time, heightened by the constant uncertainty concerning the baby's survival. By informing our knowledge of factors associated with mortality, this study will hopefully improve counselling of mothers during admission and thus alleviate some anxiety.

The patients, being mother-newborn pairs, were not involved in the study design. Every new-born admitted in our wards during the study period was assessed for inclusion in our study, no recruitment from the patient's side was necessary. The results of this study are verbally communicated to the mothers and/or caretakers, during their high-risk baby follow-up appointments.

Statistical analysis:

Demographic data is presented as frequencies (percentages) for categorical data, and as means (SD) for continuous data. To test for association between the outcome variable (mortality) and the predictor variables, a log binomial regression model was used. In order to investigate the relationship between hypertension and mortality in babies in more detail, a multiple regression model was used, adjusting for IUGR and gestational age. The standard for significance for all analyses was a p-value <0.05. Data were analysed using STATA version 15.

Results:

During the study period 4 342 babies were born in the hospital, 4 210 of these were live births and 231 (5.3%) were born with a birth weight between 500g and 1500g. Of those 231 VLBW infants, only 173 were admitted in our neonatal high care ward or to PICU. Of those, 55 died during admission, resulting in an overall mortality rate of 31.8% (95% CI: 25.2–39.2) for VLBW infants admitted to our unit. One hundred and sixty-one of the 173 VLBW infants were successfully recruited (caregivers gave informed consent) during the study period. Forty-five (28.0%) of those babies died before discharge and 116 (72.0%) were discharged home or referred to a peripheral hospital if they had reached a weight above 1500 g. For an overview of recruitment and numbers of participants, see Figure 1. All 116 babies discharged from hospital received a follow-up date for the high-risk clinic.

Demographics:

The maternal age ranged between 14 and 46 years. Fifty-eight (36.0%) mothers had HIV infection diagnosed before or during pregnancy, or at birth. Thirty-nine of them (67.2%) had been on antiretroviral (ARV) treatment at delivery for more than 4 weeks. Sixteen (27.6%) mothers had been on ARV treatment for less than 4 weeks or were not on treatment at all when giving birth, and their babies were thus considered at high risk for HIV transmission and treated accordingly. For other variables please see Table 1.

Of the 161 babies included in the study, 96 were female (59.7%). Almost all HIV exposed babies (n=58) tested negative for HIV infection at birth with a negative birth HIV-polymerase chain reaction (HIV-PCR) (n=55; 94.8%). Three babies, who died a few hours after birth, did not receive an HIV-PCR at birth and their status is therefore unknown. For other variables please see Table 2.

Table 1: Maternal demographic variables

Variables	Category	Overall* n (%)	Mortality** n (%)
Age of mother (years)	≤20	30 (18.6)	10 (33.3)
	>20	131 (81.4)	35 (26.7)
Marital status	Married/stable relationship	91 (57.6)	24 (26.4)
	No partner	67 (42.4)	18 (26.8)
Substance abuse	Yes	13 (8.1)	4 (30.8)
	No	147 (91.9)	40 (27.2)
Employment	Yes	24 (15.1)	5 (20.8)
	No	135 (84.9)	39 (28.9)
Electricity at home	Yes	143 (89.9)	41 (28.7)
	No	16 (10.1)	3 (18.8)
Running water at home	Yes	99 (62.3)	28 (28.3)
	No	60 (37.7)	16 (26.7)
Refrigerator at home	Yes	109 (68.6)	32 (29.4)
	No	50 (31.5)	12 (24.0)
Education level	Primary	72 (45.6)	22 (30.6)
	Secondary/tertiary	86 (54.4)	21 (24.4)
HIV-infection	Yes	58 (36.5)	14 (24.1)
	No	101 (63.5)	30 (29.7)
ARTs	FDC	45 (93.8)	10 (22.2)
	Second line	2 (4.2)	0 (0.0)
	Other	1 (2.1)	0 (0.0)

*The overall number and percentage per risk factor
**The number and percentage of babies who died per risk factor category.
HIV: human immunodeficiency virus, ART: antiretroviral treatment, FDC: fixed dose combination.

Table 2: Infant demographics variables

Variables	Category	Overall* n (%)	Mortality** n (%)
Gender	Female	96 (59.6)	27 (28.1)
	Male	65 (40.4)	18 (27.7)
GA (weeks)	25-32	78 (49.1)	36 (46.2)
	33-37	81 (50.9)	9 (11.1)
HIV exposed	Yes	58 (36.0)	14 (24.1)
	No	103 (64.0)	31 (30.1)
PMTCT	Yes	44 (27.3)	11 (25.0)
	No	117 (72.7)	34 (29.1)
Birth weight (g)	≤1000g	43 (26.7)	23 (53.5)
	>1000g	118 (73.3)	22 (18.6)
Born before arrival	Yes	11 (6.8)	2 (18.2)
	No	150 (93.2)	43 (28.7)

Mother not been to ANC	Yes (no ANC)	25 (15.5)	8 (32.0)
	No (ANC attended)	136 (84.5)	37 (27.2)
IUGR	Yes	111 (69.8)	23 (20.7)
	No	48 (30.2)	21 (43.8)

*The overall number and percentage per risk factor
**The number and percentage of babies who died per risk factor category.
GA: gestational age, HIV: human immunodeficiency virus, PMTCT: prevention of mother to child transmission, IUGR: intrauterine growth restriction.

Factors associated with in hospital mortality:

Maternal associated factors for the univariate model:

Univariate regression analysis was used to examine the association between mortality and associated individual factors. Associated factors of infants dying while still in hospital were higher in babies of teenage mothers, mothers with illnesses and mothers on medication. Maternal hypertension and preeclampsia were associated with decreased mortality in the babies. Education level of the mother and other socio-economic status factors were not significantly related to a higher mortality risk during admission in our study, with employment status only showing a trend towards significance (Table 3).

Table 3: Significant univariate associations between VLBW infant mortality and maternal-related factors.

Variables	**Category**	**Risk Ratio (95% CI)**	**P value**
Age of mother (years)	≤20 vs >20	1.25 (1.07- 1.45)	0.004
Hypertension	Yes vs no	0.62 (0.49 - 0.77)	<0.0001
Pre-eclampsia	Yes vs no	0.69 (0.57 - 0.82)	<0.0001
Other illnesses	Yes vs no	1.34 (1.04 - 1.74)	0.023
Medication	Yes vs no	0.43 (0.25 - 0.77)	0.004
Employment	Yes vs no	0.72 (0.52 - 1.01)	0.055
Fridge	Yes vs no	1.22 (1.01 - 1.48)	0.038

Other illnesses included malignancies, epilepsy, mental health disorders. Medication included all other medication besides antiretroviral treatment. CI: confidence interval. Most maternal factors that were not significantly associated with mortality in the regression analysis are not shown in this table.

Neonatal-associated factors:

There were many significant neonatal-associated factors related to infant mortality, such as low gestational age (p<0.0001), low birth weight (p<00001), IUGR (p<0.0001), and the need

for resuscitation at birth (p<0.0001) or during hospital stay (p=0.011). Male gender was not associated with higher mortality risk (p=0.935; RR=1.0; 95% CI: 0.7–1.5) (Table 4).

Table 4: Significant univariate associations between infant mortality and infant-related factors of VLBW infants

Variables	Category	Risk Ratio (95% CI)	P value
Gender	Female vs Male	1.02 (0.70, 1.48)	0.935
GA (weeks)	25-32 vs 33-37	4.15 (2.93, 5.88)	<0.0001
HIV exposed	No vs yes	1.25 (1.00, 1.56)	0.053
Birth weight (g)	≤1000 vs >1000	2.87 (2.08, 3.96)	<0.0001
IUGR	Yes vs no	0.47 (0.35, 0.65)	<0.0001
Resuscitation at birth	Yes vs no	4.45 (3.43, 5.78)	<0.0001
Apgar 1 min	0-6 vs 7-10	2.46 (1.99, 3.05)	<0.0001
Apgar 5 min.	0-6 vs 7-10	2.42 (2.12, 2.77)	<0.0001
HMD	Yes vs no	2.03 (1.72, 2.38)	<0.0001
Other	Yes vs no	1.59 (1.20, 2.09)	0.001
Oxygen support	Yes vs no	9.68 (7.39, 12.68)	<0.0001
Days on oxygen	0-1 day vs >1 day	1.44 (0.94, 2.21)	0.091
Surfactant given	Yes vs no	3.59 (2.77, 4.65)	<0.0001
Weight gain	Yes vs no	3.39 (2.21, 5.19)	<0.0001
Sepsis	Yes vs no	6.41 (3.78, 10.88)	<0.0001
ICH	Yes vs no	5.19 (3.03, 8.90)	<0.0001
PDA	No vs yes	2.83 (1.47, 5.47)	0.002
Resuscitation needed stay	Yes vs no	12.31 (5.85, 25.88)	0.011

GA: gestational age, HIV: human immunodeficiency virus, IUGR: intrauterine growth restriction, HMD: hyaline membrane disease, ICH: intracranial haemorrhage, PDA: persistent ductus arteriosus, ANC: antenatal clinic, Other: other problems like neonatal jaundice, hypoglycaemia, necrotizing enterocolitis, hypothermia. CI: confidence interval. Infant-related factors that were not significantly associated with mortality in the univariate regression analysis are not shown in this table, besides gender.

Multiple regression analysis

As could be seen in the univariate analysis, maternal hypertension was associated with decreased mortality in the babies. However, when adjusting for IUGR and gestational age in the multiple regression analysis, no significant association was found for maternal hypertension (p=0.279; RR=0.88; 95% CI: 0.70-1.11), as shown in Table 5.

Table 5: Results of maternal and infant factors in multiple regression analysis

Variables	Category	Risk Ratio (95% CI)	P value
Hypertension	Yes vs No	0.88 (0.70, 1.11)	0.279
IUGR	Yes vs No	1.88 (1.68, 2.11)	0.032
GA (weeks)	25-32 vs 33-37	3.80 (2.43, 5.96)	<0.0001

GA: gestational age, IUGR: intrauterine growth restriction. CI: confidence interval.

Discussion:

The prevalence of VLBW infants of all live birth in this single hospital study in the Eastern Cape Province between December 2017 and November 2018 was 5.4%. This figure lies within the prevalence of 3–7% reported worldwide (3,13), but is likely elevated due to the referrals from obstetric units and surrounding district hospitals.

Almost 32% of all admitted VLBW neonates died before discharge. For infants with a birth weight of 1000g or less this number rose to 60%, while the chance for survival of infants weighing 1000g and up to 1500g at birth was higher, with a mortality rate of 18.5%. Thus, the overall mortality rate is higher than the reported average of approximately 25% in major cities in South Africa, (24,36,37) and much higher than in the hospitals with much greater resources from the Western Cape Province (22). It is also much higher than in most hospitals in high-income countries where mortality rates for VLBW infants are as low as 9.5% to 17.2% (14,17–19). The high mortality in our setting is most likely due to the scarcity of skilled health care workers, limited infrastructures, as well as a patient overloaded, resource-restricted system, as described (4). The data support that although South Africa is considered an upper-middle-income country by the World Bank, survival of VLBW varies greatly dependent on resources (22).

Consistent with other studies examining the causes of mortality in VLBW babies, birth weight and low gestational age were predictors of neonatal mortality in our study population (18,23,26,35). Complications of prematurity, such as the development of hyaline membrane disease (HMD) and the associated need for surfactant replacement therapy with ventilation was associated with a significantly increased risk of mortality, as reported in previous research (3,22,23,26). Other studies have shown that CPAP and/or surfactant replacement therapy reduce mortality in VLBW and/or preterm neonates with hyaline membrane disease (22,41). Unavailability of PICU beds and overcrowding in our high care unit with low nurse-infants' ratio could explain why we were unable to find this benefit in our cohort.

Interestingly, our study did not find that the wide range of maternal factors found in other studies increased in-hospital mortality of infants, including lack of antenatal care, maternal primi-parity, mode of delivery or complications thereof (23,27,28,32).

Although a substantial percentage (36%) of the babies were born to HIV infected mothers, and 13.8% (n=8) of those had not received any ART before giving birth, all HIV-PCR done were negative. This is encouraging, but further research is needed to investigate HIV transmission rates in VLBW babies in low resource settings (34,35).

There are several limitations to this study. Even though this was a prospective study, data collection was not exhaustive and some prenatal variables could not be explored due to lack of information. Also, due to staff shortage, ultrasound of the head was not performed routinely, but only in clinically suspicious situations, and thus intracranial pathologies might have been missed. Furthermore, this is a single, large hospital-based study, therefore the number of VLBW cases is limited.

Conclusion

Our cohort shows a higher in-hospital mortality of VLBW infants compared to some other urban hospitals in South Africa. These findings indicate that the survival of VLBW and especially ELBW babies are still unacceptably low in this resource restricted public hospital. This is most likely caused by numerous factors, many of which have also been implicated in similar studies, but need to be further investigated in future research and appropriately addressed.

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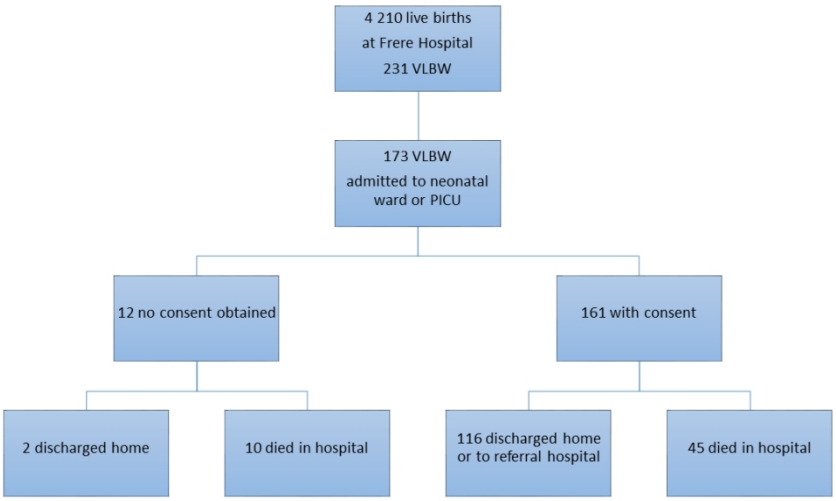
4 210 live births
at Frere Hospital
231 VLBW
173 VLBW
admitted to neonatal ward or PICU
12 no consent obtained
161 with consent
2 discharged home
10 died in hospital
116 discharged home or to referral hospital
45 died in hospital

FNo:

Data of child at birth:

Date of birth:	□		
Gender	□ female	□ male	
Gestational age:	□		
Mode of delivery:	□ NVD	□ Sectio	□ Vacuum or forceps
HIV exposed:	□ exposed	□ unexposed	
PMTCT	□ yes	□ no	
Birth weight:	gr		
Length:	cm		
Head circumferences:	cm		
Resuscitation at birth:	□ yes	□ no	
APGAR	1min	5 min	10 min
Diagnosis at birth:			
Oxygen support	□ yes	□ no	
Surfactant:	□ yes	□ no	
Ventilatory support:	□ none	□ CPAP	□ Invasive ventilation
If yes, how long	days		
Maximum of oxygen needed:	□ < 60%	□ > 60%	
Feeding option	□ Breast	□ formula	□ mixed
Trend of weight gain:	□ normal	□ abnormal	
Sepsis :	□ yes	□ no	
PVL or IVH:	□ yes	□ no	
PDA:	□ yes	□ no	
Steroid use (postnatal):	□ yes	□ no	
Resuscitation during hospital stay:	□ yes	□ no	

Mother's Data:

Age of mother:

Number of pregnancy: □

Children alive: □

Marital status: □ married □ stable relationship □ single

During pregnancy:

Hypertension: □ yes □ no

PT rupture of membranes: □ yes □ no

Preeclampsia/ Eclampsia □ yes □ no

Any other problems (e.g. seizures, drug abuse, diabetes)

SES of mother: □ employed □ unemployed

Electricity at home: □ yes □ no

Running water at home: □ yes □ no

Fridge: □ yes □ no

Educational level: □ primary school □ matric □ tertiary education

Mother's HIV status: □ positive □ negative

If positive:

ARVs since when: weeks before birth

ARVS: □ FDC □ second line □ other

Disclosure to anyone:

Has partner been tested:

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Title Page

Prospective cohort study of mortality in very low birth weight infants in a single centre in the Eastern Cape Province, South Africa

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Prospective cohort study of mortality in very low birth weight infants in a single centre in the Eastern Cape Province, South Africa

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Dr Isabel Michaelis' contribution consisted of funding acquisition, study design, investigation, data curation, supervision and drafting the initial manuscript.

Dr Ncomeka Mayisane contributed to study design, investigation, data curation and reviewing the manuscript.

Prof Ingeborg Krägeloh-Mann contributed to supervision, writing and reviewing the final manuscript.

Mrs Mikateko Mazinu contributed to data curation and data analysis.

Mrs Esme Jordaan contributes to data curation and data analysis and writing and reviewing the final manuscript.

What is known about this topic?

The perinatal mortality rate in sub-Saharan Africa is about 30 per 1000 live births. Preterm and VLBW infants account for a large number of neonatal deaths. Although South Africa is considered an upper-middle-income country by the World Bank, survival of VLBW varies greatly dependent on resources. Survival of VLBW infants in studies from South Africa are about 75%.

What does this study add?

Survival of VLBW infants fulfilling inclusion criteria for the study was 68%. Survival for VLBW babies in our setting is lower than in other South African urban settings.

Background:

Neonatal mortality is a major contributor worldwide to the number of deaths in children under 5 years of age. The primary objective of this study was to assess the overall mortality rate of babies with a birth weight equal or below 1500g in a neonatal unit at a tertiary hospital in the Eastern Cape Province, South Africa. Furthermore, different maternal and infant related factors for higher mortality were analysed.

Methods:

This is a prospective cohort study which included infants admitted to the neonatal wards of the hospital within their first 24 hours of life and with a birth weight equal to or below 1500g. Mothers who consented answered a questionnaire to identify factors for mortality.

Results:

173 very low birth weight (VLBW) infants were admitted to the neonatal department between November 2017 and December 2018, of whom 55 died (overall mortality rate 32.0%). Twenty-three of the 44 infants (53,5%) with a birth weight below 1000g died during admission. One hundred and sixty-one mothers completed the questionnaire and 45 of their babies died.

Main factors associated with mortality were lower gestational age and lower birth weight. Need for ventilator support and sepsis were associated with higher mortality, as were maternal factors such as HIV infection and age below 20 years.

Conclusion:

This prospective study looked at survival of very low birth weight babies in an underprivileged part of the Eastern Cape of South Africa. Compared to other public urban hospitals in the country the survival rate remains unacceptably low. Further research is required to find the associated causes and appropriate ways to address these.

Introduction:

Despite improved survival rates of neonates worldwide, the survival of preterm and low birth weight babies is still a challenge, especially in middle- and low-income countries (1–4).

In 2018, the World Health Organisation (WHO) described a worldwide increase of babies born prematurely over the last two decades. The incidence has been estimated between 5 to 18% of all life births (5,6). The prevalence of babies born with a very low birth weight (VLBW) varies between different countries. For example, in one South African study the prevalence was 3%, while in the USA it lies between 1.23 and 1.43% (7–9). Furthermore, prematurity and low birth weight have been identified as the leading causes of mortality in children less than five years of age (5,10–12). It is also well known that neonatal mortality for VLBW infants varies considerably amongst high- and low-middle income countries: a mortality rate of 15% is found in the United States (13), 20% by the Vermont Oxford network (14), 29.1% in Iran (3), 28.2% in South Korea (11), 32% in the Eastern Mediterranean Region (15), and 24.6% in India (16). Some single centres worldwide show a lower mortality rate with 9.5%, 12.4%, 13.0% and 17.2% in single centres in Singapore, Taiwan, Hong-Kong, Saudi-Arabia, respectively (14,17–19).

In South Africa, neonatal mortality accounted for 32% of the under-5 mortality rate (4,20,21). A recent study illustrated survival rates of VLBW neonates between different hospitals in the Western Cape Province of South Africa as characterized by unrestricted or restricted resources (22). The team found a significant difference with a survival rate of 84.4% and 70.4% respectively (22). Kalimba and Ballot (23) studied the survival rate of extremely low birth weight (ELBW) babies (babies weighing less than 1000g at birth) born between 2006 and 2010 in Johannesburg and found that only 25.6% of babies born with a birth weight of less than 900g survived their hospital stay, with birth weight and gestational age being the strongest predictors for survival. A newer retrospective cross-sectional South African study found an overall survival rate in VLBW babies (500g–1499g) of 75.7% (24).

However, there are also other known contributory factors, which can be divided into infant-or maternal-related risk factors. Examples of neonate-related risk factors studied in the literature include low Apgar scores, hyaline membrane disease (HMD), intubation and mechanical ventilation, sepsis, and hemodynamic instability (25,26). Maternal or obstetric risk factors include eclampsia, alcohol consumption, smoking, low socioeconomic status, scarce antenatal care and human immunodeficiency virus (HIV) infection (18,23,27,28). Several studies suggest an increased risk of premature labour in mothers taking antiretroviral treatment for HIV infection during pregnancy (29–32), while others did not find a relationship (33). This is noteworthy, as 30.8% of pregnant women in South Africa tested

positive for HIV in 2015, and are put on treatment as soon as the infection is diagnosed (34,35).

The primary aim of this study was to research neonatal mortality of VLBW infants admitted to the neonatal unit in a hospital in a mixed urban and rural setting in the Eastern Cape Province of South Africa. Secondly, the association between death and different maternal and neonatal factors were explored.

Setting:

Frere Hospital is a large (885 beds) public tertiary hospital in East London in the Eastern Cape Province in South Africa, with a seven-bed paediatric intensive care unit (PICU), which cares for neonates and paediatric medical and surgical patients. Because of this very limited PICU access, babies with a weight below 1000g are not provided with invasive ventilatory support due to poor survival. These babies will receive surfactant if needed and continuous positive airway pressure (CPAP) ventilation is available for six infants in the high care neonatal unit, which can cater for 12 infants altogether. This high care ward is constantly above capacity, often having to care for up to 20 infants, when there is only adequate space for the above-mentioned 12 neonates. Infants with a birth weight over 1000g will be taken to PICU and receive invasive ventilation if needed and if space is available for them. Stable neonates with a weight of more than 1000g are referred to the general nursery ward, where they receive kangaroo care (KMC) in the ward and, if necessary, intravenous fluids and/or antibiotics and oxygen. Once clinically stable, off oxygen support, tolerating full enteral feeds and weighing more than 1500g, infants will be transferred to the KMC ward until mothers are competent in caring for their baby and the weight has increased to at least 1700 g. Some stable babies might be transferred to their regional hospital once their weight has reached 1500g.

Frere Hospital is the tertiary neonatal and obstetric referral centre for obstetric units and for surrounding district hospitals in the middle part of the Eastern Cape Province. Some referrals centres are more than 300 km away. These areas were deprived of adequate infrastructure during the Apartheid regime and are still one of the most under-resourced and insufficiently managed parts of South Africa.

Materials and Methods:

This was a prospective cohort study. All babies born at the hospital, or admitted within the first 24 hours of life into the neonatal unit, with a birth weight equal or below 1500g and without any life-threatening malformations were included. Neonates who were admitted to

the neonatal ward or PICU beyond 24 hours of life were excluded as it was not possible to get sufficient information on those mother-infant pairs. Mothers were then approached for consent to include their data. The recruitment period lasted from December 2017 to November 2018.

The study was approved by the institutional ethics committee (086/2017) and, after receiving written consent from the mothers, data concerning mother and child during the pre-, peri- and neonatal period were collected from the maternal and neonatal case records, as well as from a questionnaire filled in with the mother (see supplements). The babies were followed up until discharge or death. All babies received standard care during this period, as outlined above.

Gestational age was determined by either an early ultrasound or by applying the Ballard gestational age scoring system. It is estimated that about 70% of the babies admitted to our neonatal wards will have had their gestational age assessed by early ultrasound. The different variables were defined as follows: a persistent ductus arteriosus as identified by echocardiogram; hyaline membrane disease by the presence respiratory distress; FiO_2 requirement above 40% followed by a confirmatory blood gas and typical X-ray signs; sepsis as clinical signs confirmed with a positive blood, urine or cerebrospinal fluid culture and/or raised C-reactive protein (CRP) taken at least 24 hours apart; normal weight gain was determined when weight loss after birth did not exceed more than 10% and birth weight was regained within 10-14 days of life; intracranial haemorrhage (ICH) was diagnosed with cranial ultrasound, which was only performed in clinically unstable infants with the clinical suspicion of ICH; resuscitation at birth included mask or invasive ventilation with or without cardiac compressions and medication.

Patient and Public Involvement:

The patients, being mother-newborn pairs, were not involved in the study design. Every new-born admitted in our wards during the study period was assessed for inclusion in our study, no recruitment from the patient's side was necessary. The results of this study are verbally communicated to the mothers and/or caretakers.

Statistical analysis:

Demographic data is presented as frequencies (percentages) for categorical data, and as means (SD) for continuous data. To test for association between the outcome variable

(mortality) and the predictor variables, a log binomial regression model was used. In order to investigate the relationship between hypertension and mortality in babies in more detail, a multiple regression model was used, adjusting for IUGR and gestational age. The standard for significance for all analyses was a p-value <0.05. Data were analysed using STATA version 15.

Results:

During the study period 4 342 babies were born in the hospital, 4 210 of these were live births and 231 (5.3%) were born with a birth weight between 500g and 1500g. Of those 231 VLBW infants, only 173 met the inclusion criteria for the study. Of those, 55 died during admission, resulting in an overall mortality rate of 31.8% (95% CI: 25.2–39.2) for VLBW infants admitted to our unit.

One hundred and sixty-one of the 173 VLBW infants were successfully recruited (caregivers gave informed consent) during the study period. Forty-five (28.0%) of those babies died before discharge and 116 (72.0%) were discharged home or referred to a peripheral hospital if they had reached a weight above 1500 g. Forty-four of the 161 babies were born with a birth weight below 1000g, of those 23 (53,5%) did not survive until discharge. For an overview of recruitment and numbers of participants, see Figure 1. All 116 babies discharged from hospital received a follow-up date for the high-risk clinic.

Demographics:

The maternal age ranged between 14 and 46 years. Fifty-eight (36.0%) mothers had HIV infection diagnosed before or during pregnancy, or at birth. Thirty-nine of them (67.2%) had been on antiretroviral (ARV) treatment at delivery for more than 4 weeks. Sixteen (27.6%) mothers had been on ARV treatment for less than 4 weeks or were not on treatment at all when giving birth, and their babies were thus considered at high risk for HIV transmission and treated accordingly. For other variables please see Table 1.

Of the 161 babies included in the study, 96 were female (59.7%). Almost all HIV exposed babies (n=58) tested negative for HIV infection at birth with a negative birth HIV-polymerase chain reaction (HIV-PCR) (n=55; 94.8%). Three babies, who died a few hours after birth, did not receive an HIV-PCR at birth and their status is therefore unknown. For other variables please see Table 2.

Table 1: Maternal demographic variables

Variables	Category	Overall* n =161 (%)	Neonates who died ** N=45 (%)
Age of mother (years)	≤20	30 (18.6)	10 (33.3)
	>20	131 (81.4)	35 (26.7)
Marital status	Married/stable relationship	91 (57.6)	24 (26.4)
	No partner	67 (42.4)	18 (26.8)
Substance abuse	Yes	13 (8.1)	4 (30.8)
	No	147 (91.9)	40 (27.2)
Employment	Yes	24 (15.1)	5 (20.8)
	No	135 (84.9)	39 (28.9)
Electricity at home	Yes	143 (89.9)	41 (28.7)
	No	16 (10.1)	3 (18.8)
Running water at home	Yes	99 (62.3)	28 (28.3)
	No	60 (37.7)	16 (26.7)
Refrigerator at home	Yes	109 (68.6)	32 (29.4)
	No	50 (31.5)	12 (24.0)
Education level	Primary	72 (45.6)	22 (30.6)
	Secondary/tertiary	86 (54.4)	21 (24.4)
HIV-infection	Yes	58 (36.5)	14 (24.1)
	No	101 (63.5)	30 (29.7)
ARTs	FDC	45 (93.8)	10 (22.2)
	Second line	2 (4.2)	0 (0.0)
	Other	1 (2.1)	0 (0.0)

*The overall number and percentage per risk factor
**The number and percentage of babies who died per risk factor category.
HIV: human immunodeficiency virus, ART: antiretroviral treatment, FDC: fixed dose combination.

Table 2: Infant demographics variables

Variables	Category	Overall* n =161 (%)	Neonates who died ** N=45 (%)
Gender	Female	96 (59.6)	27 (28.1)
	Male	65 (40.4)	18 (27.7)
GA (weeks)	25-32	78 (49.1)	36 (46.2)
	33-37	81 (50.9)	9 (11.1)
HIV exposed	Yes	58 (36.0)	14 (24.1)
	No	103 (64.0)	31 (30.1)
PMTCT	Yes	44 (27.3)	11 (25.0)
	No	117 (72.7)	34 (29.1)
Birth weight (g)	≤1000g	43 (26.7)	23 (53.5)
	>1000g	118 (73.3)	22 (18.6)
Born before arrival	Yes	11 (6.8)	2 (18.2)
	No	150 (93.2)	43 (28.7)
Mother not been to ANC	Yes (no ANC)	25 (15.5)	8 (32.0)

	No (ANC attended)	136 (84.5)	37 (27.2)
IUGR	Yes	111 (69.8)	23 (20.7)
	No	48 (30.2)	21 (43.8)

*The overall number and percentage per risk factor
**The number and percentage of babies who died per risk factor category.
GA: gestational age, HIV: human immunodeficiency virus, PMTCT: prevention of mother to child transmission, IUGR: intrauterine growth restriction.

Factors associated with in hospital mortality:

Maternal associated factors for the univariate model:

Univariate regression analysis was used to examine the association between mortality and associated individual factors. Associated factors of infants dying while still in hospital were higher in babies of teenage mothers, mothers with illnesses and mothers on medication. Maternal hypertension and preeclampsia were associated with decreased mortality in the babies. Education level of the mother and other socio-economic status factors were not significantly related to a higher mortality risk during admission in our study, with employment status only showing a trend towards significance (Table 3).

Table 3: Significant univariate associations between VLBW infant mortality and maternal-related factors.

Variables	**Category**	**Risk Ratio (95% CI)**	**P value**
Age of mother (years)	≤20 vs >20	1.25 (1.07- 1.45)	<0.01
Hypertension	Yes vs no	0.62 (0.49 - 0.77)	<0.01
Pre-eclampsia	Yes vs no	0.69 (0.57 - 0.82)	<0.01
Other illnesses	Yes vs no	1.34 (1.04 - 1.74)	0.02
Medication	Yes vs no	0.43 (0.25 - 0.77)	<0.01
Employment	Yes vs no	0.72 (0.52 - 1.01)	0.06
Fridge	Yes vs no	1.22 (1.01 - 1.48)	0.04

Other illnesses included malignancies, epilepsy, mental health disorders. Medication included all other medication besides antiretroviral treatment. CI: confidence interval. Most maternal factors that were not significantly associated with mortality in the regression analysis are not shown in this table.

Neonatal-associated factors:

There were many significant neonatal-associated factors related to infant mortality, such as low gestational age (p<0.01), low birth weight (p<0.01), IUGR (p<0.01), and the need for

resuscitation at birth (p<0.01) or during hospital stay (p=0.01). Male gender was not associated with higher mortality risk (p=0.94; RR=1.0; 95% CI: 0.7–1.5) (Table 4).

Table 4: Significant univariate associations between infant mortality and infant-related factors of VLBW infants

Variables	Category	Risk Ratio (95% CI)	P value
Gender	Female vs Male	1.02 (0.70, 1.48)	0.94
GA (weeks)	25-32 vs 33-37	4.15 (2.93, 5.88)	<0.01
HIV exposed	No vs yes	1.25 (1.00, 1.56)	0.05
Birth weight (g)	≤1000 vs >1000	2.87 (2.08, 3.96)	<0.01
IUGR	Yes vs no	0.47 (0.35, 0.65)	<0.01
Resuscitation at birth	Yes vs no	4.45 (3.43, 5.78)	<0.01
Apgar 1 min	0-6 vs 7-10	2.46 (1.99, 3.05)	<0.01
Apgar 5 min.	0-6 vs 7-10	2.42 (2.12, 2.77)	<0.01
HMD	Yes vs no	2.03 (1.72, 2.38)	<0.01
Other	Yes vs no	1.59 (1.20, 2.09)	0.01
Oxygen support	Yes vs no	9.68 (7.39, 12.68)	<0.01
Days on oxygen	0-1 day vs >1 day	1.44 (0.94, 2.21)	0.09
Surfactant given	Yes vs no	3.59 (2.77, 4.65)	<0.01
Weight gain	Yes vs no	3.39 (2.21, 5.19)	<0.01
Sepsis	Yes vs no	6.41 (3.78, 10.88)	<0.01
ICH	Yes vs no	5.19 (3.03, 8.90)	<0.01
PDA	No vs yes	2.83 (1.47, 5.47)	<0.01
Resuscitation needed stay	Yes vs no	12.31 (5.85, 25.88)	0.01

GA: gestational age, HIV: human immunodeficiency virus, IUGR: intrauterine growth restriction, HMD: hyaline membrane disease, ICH: intracranial haemorrhage, PDA: persistent ductus arteriosus, ANC: antenatal clinic, Other: other problems like neonatal jaundice, hypoglycaemia, necrotizing enterocolitis, hypothermia. CI: confidence interval. Infant-related factors that were not significantly associated with mortality in the univariate regression analysis are not shown in this table, besides gender.

Multiple regression analysis

As could be seen in the univariate analysis, maternal hypertension was associated with decreased mortality in the babies. However, when adjusting for IUGR and gestational age in the multiple regression analysis, no significant association was found for maternal hypertension (p=0.28; RR=0.88; 95% CI: 0.70-1.11), as shown in Table 5.

Table 5: Results of maternal and infant factors in multiple regression analysis

Variables	Category	Risk Ratio (95% CI)	P value
Hypertension	Yes vs No	0.88 (0.70, 1.11)	0.28
IUGR	Yes vs No	1.88 (1.68, 2.11)	0.03
GA (weeks)	25-32 vs 33-37	3.80 (2.43, 5.96)	<0.01

GA: gestational age, IUGR: intrauterine growth restriction. CI: confidence interval.

Discussion:

The prevalence of VLBW infants of all live birth in this single hospital study in the Eastern Cape Province between December 2017 and November 2018 was 5.4%. This figure lies within the prevalence of 3–7% reported worldwide (3,13), but is likely elevated due to the referrals from obstetric units and surrounding district hospitals.

Almost 32% of all admitted VLBW neonates died before discharge. For infants with a birth weight of 1000g or less this number rose to 60%, while the chance for survival of infants weighing 1000g and up to 1500g at birth was higher, with a mortality rate of 18.5%. Thus, the overall mortality rate is higher than the reported average of approximately 25% in major cities in South Africa, (24,36,37) and much higher than in the hospitals with much greater resources from the Western Cape Province (22). It is also much higher than in most hospitals in high-income countries where mortality rates for VLBW infants are as low as 9.5% to 17.2% (14,17–19,38,39). The high mortality in our setting is most likely due to the scarcity of skilled health care workers, limited infrastructures, as well as a patient overloaded, resource-restricted system, as described (4). The data supports that although South Africa is considered an upper-middle-income country by the World Bank, survival of VLBW varies greatly dependent on resources (22).

Consistent with other studies examining the causes of mortality in VLBW babies, birth weight and low gestational age were predictors of neonatal mortality in our study population (18,23,26,35). Complications of prematurity, such as the development of hyaline membrane disease (HMD) and the associated need for surfactant replacement therapy with ventilation was associated with a significantly increased risk of mortality, as reported in previous research (3,22,23,26). Other studies have shown that CPAP and/or surfactant replacement therapy reduce mortality in VLBW and/or preterm neonates with hyaline membrane disease (22,40). Unavailability of PICU beds and overcrowding in our high care unit with low nurse-infants' ratio could explain why we were unable to find this benefit in our cohort.

Interestingly, our study did not find that the wide range of maternal factors found in other studies increasing in-hospital mortality of infants, including lack of antenatal care, maternal primi-parity, mode of delivery or complications thereof (23,27,28,32).

Although a substantial percentage (36%) of the babies were born to HIV infected mothers, and 13.8% (n=8) of those had not received any ART before giving birth, all HIV-PCR done were negative. This is encouraging, but further research is needed to investigate HIV transmission rates in VLBW babies in low resource settings (34,35).

There are several limitations to this study. Even though this was a prospective study, data collection was not exhaustive and some prenatal variables could not be explored due to lack of information. Also, due to staff shortage, ultrasound of the head was not performed routinely, but only in clinically suspicious situations, and thus intracranial pathologies might have been missed. Furthermore, this is a single hospital-based study, therefore the number of VLBW cases is limited.

Conclusion

Our cohort shows a higher in-hospital mortality of VLBW infants compared to some other urban hospitals in South Africa. These findings indicate that the survival of VLBW and especially ELBW babies are still unacceptably low in this resource restricted public hospital. This is most likely caused by numerous factors, many of which have also been implicated in similar studies, but need to be further investigated in future research and appropriately addressed.

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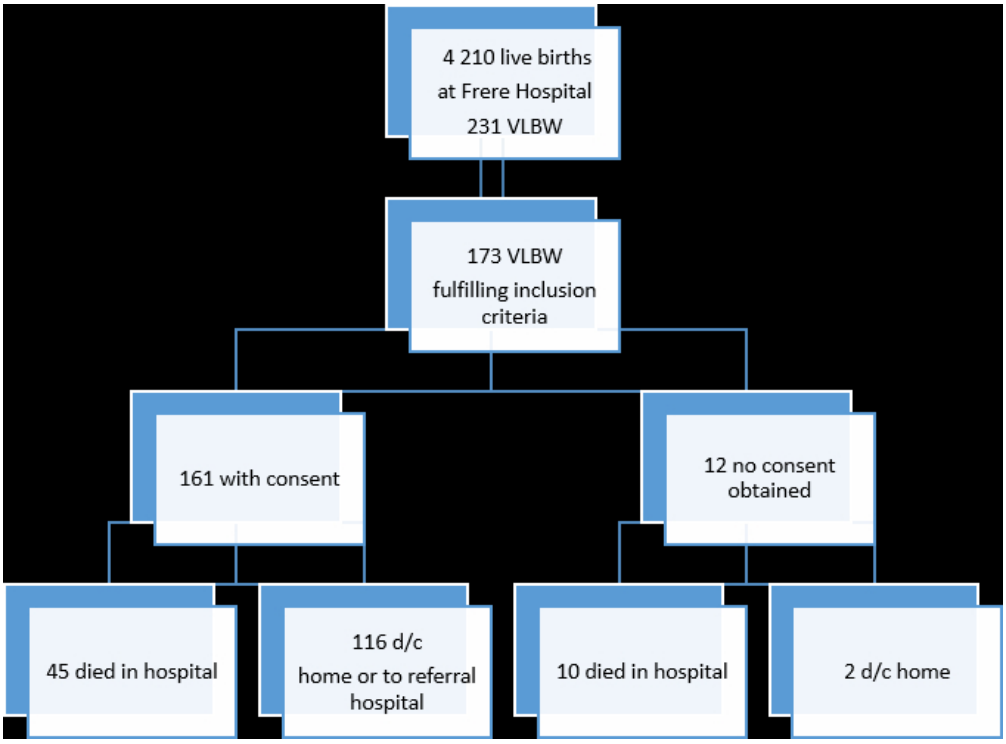
4 210 live births
at Frere Hospital
231 VLBW
173 VLBW
fulfilling inclusion
criteria
161 with consent
12 no consent
obtained
45 died in hospital
116 d/c
home or to referral
hospital
10 died in hospital
2 d/c home

FNo:

Data of child at birth:

Date of birth:	□		
Gender	□ female	□ male	
Gestational age:	□		
Mode of delivery:	□ NVD	□ Sectio	□ Vacuum or forceps
HIV exposed:	□ exposed	□ unexposed	
PMTCT	□ yes	□ no	
Birth weight:	gr		
Length:	cm		
Head circumferences:	cm		
Resuscitation at birth:	□ yes	□ no	
APGAR	1min	5 min	10 min
Diagnosis at birth:			
Oxygen support	□ yes	□ no	
Surfactant:	□ yes	□ no	
Ventilatory support:	□ none	□ CPAP	□ Invasive ventilation
If yes, how long	days		
Maximum of oxygen needed:	□ < 60%	□ > 60%	
Feeding option	□ Breast	□ formula	□ mixed
Trend of weight gain:	□ normal	□ abnormal	
Sepsis :	□ yes	□ no	
PVL or IVH:	□ yes	□ no	
PDA:	□ yes	□ no	
Steroid use (postnatal):	□ yes	□ no	
Resuscitation during hospital stay:	□ yes	□ no	

Mother's Data:

Age of mother:

Number of pregnancy: □

Children alive: □

Marital status: □ married □ stable relationship □ single

During pregnancy:

Hypertension: □ yes □ no

PT rupture of membranes: □ yes □ no

Preeclampsia/ Eclampsia □ yes □ no

Any other problems (e.g. seizures, drug abuse, diabetes)

SES of mother: □ employed □ unemployed

Electricity at home: □ yes □ no

Running water at home: □ yes □ no

Fridge: □ yes □ no

Educational level: □ primary school □ matric □ tertiary education

Mother's HIV status: □ positive □ negative

If positive:

ARVs since when: weeks before birth

ARVS: □ FDC □ second line □ other

Disclosure to anyone:

Has partner been tested: