Short-term mortality and morbidity of very-low birth weight infants over 9 years at Groote Schuur Hospital

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DECLARATION

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Short-term mortality and morbidity of very-low birth weight infants over 9 years at Groote Schuur Hospital

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Abstract

Background: With the advancement of neonatal care there has been a decrease in mortality rates of VLBW infants worldwide. However, this has been at the cost of increased morbidity in this vulnerable group. Currently there are little up to date data on short term morbidities for VLBW infants in low and middle-income countries.

Objectives: The primary objective was to describe the neonatal mortality rate in infants 401g-1500g admitted to Groote Schuur neonatal nursery over 9 years and within weight categories. Secondary objectives were to evaluate the main neonatal short-term morbidities of these infants over time and within weight categories.

Methods: This study is a secondary analysis of prospectively collected observational data. All VLBW (<1501g) infants admitted to Groote Schuur Neonatal unit from 2012-2020 were included in the study. Data were benchmarked against the Vermont Oxford Network database.

Results: Of the 4644 infants included in the study the overall mortality rate was 19.8%, which remained static over the study period and was higher in comparison to the VON. There was a significantly higher mortality rate associated with decreasing birth weight. The mortality rate for outborn vs inborn infants was higher: 30.3% vs 18.4% (p value 0.046). There was a significant risk of short-term morbidity in infants <1001g vs 1001- 1500g. The survival rate without major morbidity was 65.8% overall. There was a higher survival rate without morbidities with increasing birth weight. Survival rates without morbidity were comparable to that of the VON.

Conclusion: The results demonstrate that mortality rates are higher in comparison to developed countries. However, importantly, survival without morbidity is comparable. Strategies to improve mortality and morbidity in VLBW infants are multifaceted and require a collaborative and innovative approach. Important strategies include an emphasis on improved antenatal care, regionalization of care, screening facilities, neonatal specific training of staff, antenatal steroids, CPAP, surfactant replacement therapy, stringent infection control procedures, kangaroo mother care and promotion of breastfeeding.

Introduction:

Preterm births are a global public health issue with 15 million occurring annually worldwide, with over 81% of these occurring in Sub-Saharan Africa and South Asia [1, 2]. Preterm infants are a vulnerable subset of infants at increased risk of complications and mortality with nearly half (47%) of all under 5 deaths occurring in the first 28 days of life in 2020[3]. With the advancement of neonatal care, the neonatal mortality has declined globally with improved access to interventions such as Continuous positive airway pressure (CPAP), surfactant replacement therapy and ventilation. High income countries such as Switzerland and Sweden had neonatal mortality rates of 2.8 and 1.4/1000 live births respectively in 2020[4]. South Africa is among the many nations who have adopted the United Nations Sustainable development goals and has made progress in achieving goal 3- which pledges to end preventable deaths of newborns and to reduce neonatal mortality to at least as low as 12 per 1000 live births. South Africa's neonatal mortality rate has fallen from 28.5 deaths per 1000 live births in 1975 to 10.5 deaths per 1000 live births in 2020[4]. Notably, there are significant variations of the neonatal mortality rates across the provinces in South Africa with the highest neonatal mortality rates occurring in Gauteng and Kwa-Zulu Natal[5].

Survival of preterm infants <1500g across 10 high income countries (HIC's) was reported to be 78-93 %[6]. The USA reported survival rates of 85% [7]. South Africa is considered a middle-income country (MIC) and studies performed at two public hospitals in South Africa between 2000 and 2017 reported infant survival rates of VLBW infants to be between 72 and 75%[8, 9]. Low-income countries (LIC's) have lower survival rates. In Malawi, 42% in VLBW infants survived to discharge, with only 11% of infants <1000g surviving to discharge [10]. Ethiopia reported a survival rate of VLBW of 49% [11]. Africa consists of low- and middle-income countries (LMIC's) and faces significant health care challenges in comparison to high income countries in caring for preterm infants. There is a wide discrepancy in survival in very low birth weight infants (VLBW) infants across the African continent with limited access to resources [12, 13]. In 2020, a review of resources in 49 African countries reported that proven life-saving neonatal interventions such as CPAP, surfactant replacement therapy and saturation monitoring of infants were inadequate and inequitably distributed. This inequality was evidenced not only between countries, but also rural and

urban areas, and the public and private sectors [12]. A study done at Mowbray Maternity hospital and Groote Schuur Hospital (GSH) in infants ≤1,8kg modelled the removal of mechanical ventilation, surfactant therapy and CPAP, that predicted that their mortality rate would triple without these interventions[14].

VLBW and extremely low birth weight (ELBW) infants are at increased risk of long-term neurodevelopmental disabilities such as cerebral palsy, cognitive impairment, and visual and hearing impairments. Improved survival rates and complications of prematurity poses a significant public health challenge globally, but especially so in LMIC's where there is limited ability to provide multidisciplinary follow-up support for these families.

There is currently limited up-to-date data preterm short- and long-term morbidity outcomes in South Africa. A study done in Tshwane, showed survival without major morbidity in VLBW infants was 35% overall, (39% in the 1000g-1500g subgroup and 26% in infants <1000g)[9].

A study reviewing the literature on the indicators of neonatal morbidity found that the most common indicators used for defining neonatal morbidity were necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP)[15]. Other studies included late onset sepsis, patent ductus arteriosus (PDA) and growth failure at discharge[16].

GSH is a 75-bed state sector neonatal unit and admits over 2000 neonates per year, with ~500 being <1501g. The GSH Maternity centre is a tertiary referral centre and provides level 3 specialist care to high-risk pregnancies to the Metro West Health District in Cape Town (population 4.5 million), South Africa. The neonatal unit is one of two tertiary referral hospitals in the city for small and sick neonates. The neonatal nursery offers intensive care facilities, with 10 beds for invasive ventilation and 10 beds for non-invasive ventilation. Due to resource limitations and the high level of morbidity associated with extremely low birth weight infants, only non-invasive ventilation is offered to babies <800g or <27 weeks at Groote Schuur Hospital in line with the Western Cape provincial policy guidelines.

Vermont Oxford Network (VON) database was established in 1988 and now comprises >1400 neonatal units worldwide. This non-profit organisation aims to improve the quality of care of premature neonates through research, education, and quality improvement projects [17]. Standardized neonatal data was collected for the VON network for all neonates 401g-1500g who were admitted to Groote Schuur Neonatal unit from 2012 to 2020 (appendix A).

This study aims to evaluate the mortality and short-term morbidity of VLBW infants at Groote Schuur Hospital and to compare this data with that of Vermont Oxford Network [18]. This will contribute to the limited data available about outcomes in LMICs.

Objectives:

The primary objective was to describe the neonatal mortality rate in infants 401g - 1500g admitted to Groote Schuur neonatal nursery over time and within weight categories.
The secondary objective was to evaluate the significant short-term morbidities of these infants.

Study Design:

This is a secondary analysis of prospectively collected data over 9 years of VLBW infants between January 2012 and December 2020 at Groote Schuur Neonatal unit.

Inclusion criteria: All infants <1501g who were admitted to the NICU within 28 days of birth but also including deaths in the delivery room.

Exclusion criteria: Infants admitted after 28 days of life.

Study definitions:

Neonatal mortality was defined as death before discharge home. Small for gestational age (SGA) was defined as a birth weight below the 10^{th} centile, based on sex specific Fenton growth charts. Definitions for infant mortality and morbidity were used in accordance with those provided by the VON [18] (see appendix A). VON considers the following to be major morbidities: severe intraventricular haemorrhage (Severe IVH), periventricular leukomalacia

(PVL), Chronic lung disease (CLD) in infants < 33 weeks; necrotising enterocolitis (NEC), pneumothorax, late onset sepsis (LOS) and severe Retinopathy of prematurity (ROP) [19]. Severe IVH includes infants which have a grade 3 or 4 periventricular-intraventricular hemorrhage (PIH) on or before day 28. Grade 3 IVH is defined as intraventricular blood and ventricular dilation; Grade 4 IVH includes intraparenchymal hemorrhage. Cystic periventricular leukomalacia is diagnosed on a cranial ultrasound, CT, or MRI scan obtained at any time. To be considered cystic periventricular leukomalacia there must be multiple small periventricular cysts identified. NEC is diagnosed at surgery, at postmortem examination, or clinically and radiographically. Chronic lung disease is defined as infants < 33 Weeks post menstrual age who are on oxygen. LOS Indicates whether the infant has either Late Bacterial Infection and/or Coagulase Negative Staph and/or Fungal Infection after Day 3 of life. This is defined as confirmed culture of blood or CSF. Pneumothorax is diagnosed if the infant had extrapleural air diagnosed by chest radiograph or needle aspiration (thoracentesis). ROP indicates whether the infant has a stage 3, 4 or 5 ROP. Stage 3 includes the presence of a ridge with extraretinal fibrovascular proliferation, stage 4: Partial retinal detachment and Stage 5: Total retinal detachment.

Weight categories were used instead of gestational age due to unsure dates and gestation of our population. Only 30-40% of the mothers have early (<20 weeks) obstetric ultrasounds. The remaining infants are assigned gestational age by postnatal assessment which includes Ballard scoring and foot length [20]

Statistical Analysis:

The data were analysed using STATA/IC version 14.2 (College Stata, Tx, USA). Continuous variables were expressed as medians (interquartile range, IQR) since the continuous data were skewed. Proportions and percentages were used to describe categorical variables. The association between categorical variables was done using Pearson's Chi-square test. P-values ≤0.05 were considered statistically significant. VON median, Q1, and Q3 were computed by calculating each member hospital's mean rate over the 9 years and ranking these rates from highest to lowest. The rate at the 50^{th} percentile is the median; the rate at the 25^{th} percentile is the Q1; and the rate at the 75^{th} percentile is the Q3.

Ethical Considerations:

All data captured in the VON database are automatically de-identified and assigned a study number to ensure confidentiality. Approval for this study was obtained from the University of Cape Town Human Research Ethics Committee (HREC 505/2021).

Results:

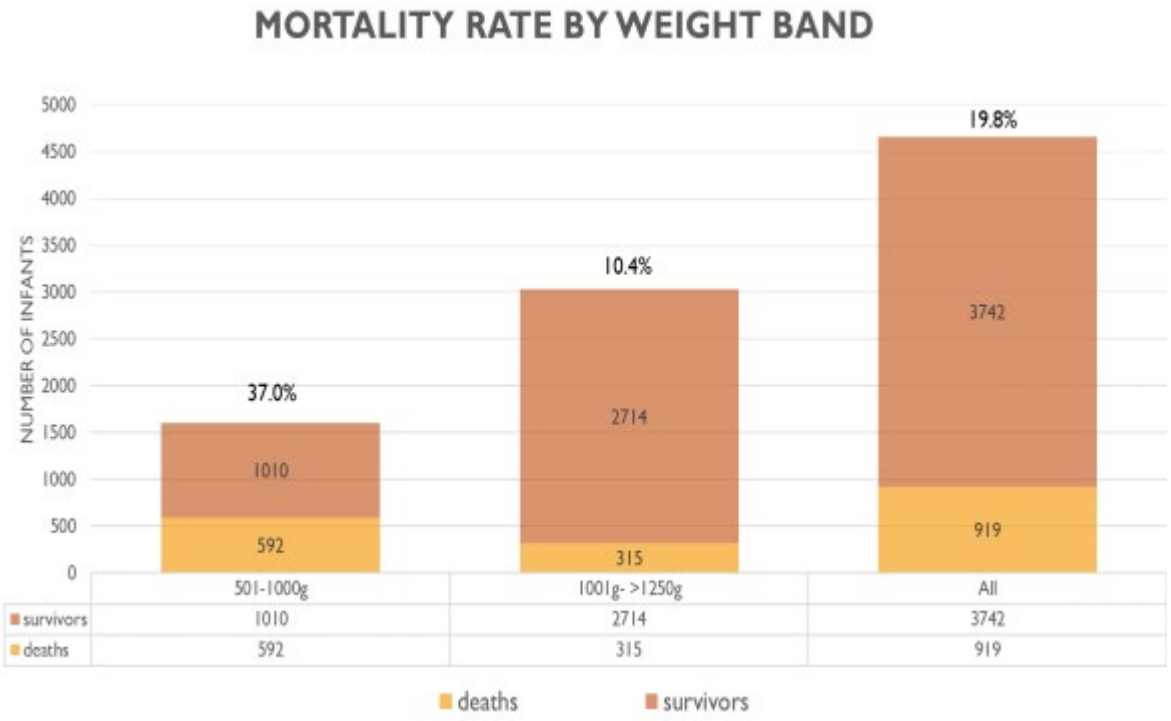
Study Cohort: A total of 4645 infants with a birth weight 401g-1500g were included in the study.

Maternal characteristics: Eighty-five percent (n=3906/4592**)** mothers had at least one antenatal visit. This proportion trended upwards over the 9 years (starting at 86.9% versus finishing 90.5 %). Over the study period, 69.3% (n=2967/4280) of the mothers <34 weeks gestation received any antenatal steroids prior to delivery. The Caesarean section rate was 67.1% (n= 3092/4608).

Infants Characteristics: Male infants comprised 47.5% of the study cohort. Overall, 27% (n=1242/4600) of the infants were SGA. Major life-threatening congenital anomalies (chromosomal or structural) were present in 121 (2.6%) of the infants, of which 80 (66%) died.

Mortality: The Infant mortality rate was 19.8% overall (**Figure 1)** with a 100% mortality rate in infants <501g; There were 25 deaths in the delivery room. The mortality rate remained relatively static over the study period. The mortality rate for inborn infants was significantly lower in comparison to outborn infants: 18.4% vs 30.3% in outborn infants (p value 0.046).

Figure 1:



Morbidities:

The main morbidities were more frequent in the ELBW infants **(Table 1)**. The two morbidities that showed the most variation were LOS and NEC which fluctuated over the study period but in no particular pattern. These values ranged from 5.2% to 10.4% (LOS) and 3.1% to 8% (NEC) over the study period.

Table 1: Mean percentage of morbidities within weight categories at GSH NICU:

2012- 2020

% Morbidities	VLBW	501-1000g	1001-1500g	p-value
Cystic PVL	2.4	3.5	1.9	0.002
Severe IVH	5.8	7.9	4.8	<0.001
NEC	5.9	8.6	4.5	<0.001
Severe ROP	3.4	7	1.5	<0.001
Pneumothorax	0.6	0.6	0.6	0.79
CLD <33w	4.5	8.7	2.6	<0.001
LOS	8.3	14.9	5.2	<0.05

Survival without morbidities: The survival rate without major morbidity was 68.5% overall. There was a higher survival rate without morbidities with increasing birth weight: 47.6% (n=763/1603) of the infants in the 501-1000g category and 79.8 % in infants 1001-1500g (n= 2419/3029).

Overall, 48.6% (n=2109/4343) of infants were moderately hypothermic (temperature of 32-35.9% within one hour of admission). Of those infants with available data, ELBW infants were more likely to be hypothermic (53.1% (809/1523) compared to VLBW infants (46.1% (1300/2820)) (p=0.001). Infants exclusively fed on breastmilk at discharge were 72.2%. The median length of stay for all surviving infants admitted between 2012 and 2020 was 43 days from admission until discharge home **(table 2).**

Table 2: Median length of stay of VLBW infants at GSH NICU 2012-2020

Median length of stay (days)			
	All	Survivors	Death
501-750g	7	73	3
751-1000g	53	60	4
1001-1250g	42	44	4
>1250g	29	29	4
All	38	43	4

Comparison to the VON Network:

Characteristics:

Compared to the median rates of VON member hospitals, exposure to antenatal steroids less than 34weeks gestation was lower (69.3% vs 86.2%), moderate hypothermia was higher (48.6% vs 10.2%), and discharge home on any human milk was higher (72.2 % vs 59.6%).

The GSH mortality rates was higher than the Q3 of the VON hospital rates. However, the death or morbidity was below the Q1. All morbidities fell within the interquartile range except for CLD<33w which was markedly lower than the Q1 for VON member hospital rates **(table 3)**.

Table 3: Mortality and morbidity vs VON network 2012 – 2020

Mortality and Morbidities vs Von 2012-2020			
	GSH	VON	
	Mean%	Mean%	Centers median and IQR
Mortality	19.8	14.1	12.3 (9.3 -16.7)
Survival with morbidity	31.5	43.6	40.0 (32.0 – 48.3)
NEC	5.9	5.2	3.6 (1.7 – 9.3)
LOS	8.3	12.3	9.5 (5.9 - 15.0)
SEVERE IVH	5.8	8.0	6.6 (3.9 – 8.9)
CYSTIC PVL	2.4	2.9	2.2 (1.1- 3.7)
SEVERE ROP	3.4	6.3	4.2 (1.5 - 7.2)
Pneumothorax	0.6	4.3	3.4 (1.9 - 5.0)
CLD <33w	4.4	26.8	21.7 (12.7- 31.1)

VON mean is the average of the network means over 9 years.

Centers median and IQR are taken from the middle year of the study (2016)

Discussion:

This study includes one of the largest cohorts of VLBW infants from a single center in a LMIC setting. Whilst South Africa is considered an upper-middle income country, we are still faced with significant discrepancies in available resources and infrastructure to combat neonatal mortality and morbidity.

The overall mortality rate for VLBW infants was 19.8% which is favourable in comparison to other studies done in South Africa, but still remains higher than that of HIC's [7-9, 21, 22]. The reason for higher mortality rates at GSH can be attributed to GSH being a tertiary referral centre for the delivery of premature infants <1500g, resulting in higher numbers of high-risk infants being born and transferred to our facility. As expected, ELBW infants were significantly more likely to die due to being more preterm and/or growth restricted. These

infants would also be the ones primarily affected by policies affecting the availability of full intensive care.

Further focus is required in tackling the socioeconomical barriers to mothers receiving antenatal care, encouraging early booking of pregnancies, and improving antenatal steroid administration to mothers with preterm labour <33w gestation. The WHO recommends the use of antenatal steroids in women at risk of preterm birth with the provision of adequate neonatal care[23, 24]. A prospective study done at GSH found that although antenatal steroid use was relatively high (74.3%), only 17.3% of mothers at risk of preterm birth received the recommended optimal regime of two doses of antenatal steroids more than 24 hours but <7 days prior to delivery[14].

Hypothermia within one hour of admission is an important area to work on as normothermia has been shown to improve outcomes of preterm infants[25]. Encouragingly, the rates of breastfeeding were higher in comparison to the VON network. The promotion of breastfeeding is an important strategy in our setting in reducing NEC, improving maternal bonding with their babies and health promotion in preterm infants post discharge.

There was increased mortality of outborn vs inborn infants confirming a previous study done at GSH[26]**.** Efforts have been made in South Africa towards regionalisation of perinatal care to ensure that high risk pregnancies are delivered at tertiary level hospitals. This policy is aimed at allowing these high-risk infants access to neonatal ICU, staff trained in neonatal care and screening facilities eg ROPS and cranial ultrasound screening. This is an important strategy to improve outcomes and minimize morbidity in preterm babies.

Whilst GSH mortality rates are higher in comparison to the VON network, our death or morbidity rates are lower mainly due to a markedly lower CLD<33w incidence. Encouragingly, over 2/3rds of infants survived to discharge without major morbidity overall, but only half of the infants 501g-1000g survived without major morbidity, highlighting the vulnerability of this subgroup of infants. Determining the limits of viability in resource limited settings is complex and remains an ongoing challenge. All categories of morbidities

were significantly higher in the infants <1001g except for pneumothorax. The prevalence of short-term morbidities remained static over the study period except for LOS and NEC, which showed variability over the study period.

Although GSH's mean percentage of NEC fell mostly within the interquartile range of the VON it was on the upper limit of the VON network data. NEC rates were almost double in infants <1000g vs infants 1001-1500g. As many of the most preterm infants do not survive long, it is worth interrogating why the NEC rate is not lower. A study previously conducted in our unit observed increased risk of adverse outcomes in HIV exposed infants with an increased risk of NEC, especially in infants < 1000g[27]. Also, the prevalence of SGA infants is higher in our setting in comparison to developed countries and is also shown to be have an increased risk of NEC and mortality[28]. It is imperative to enforce rigorous handwashing protocols, champion infection control, limit invasive procedures and prevent over-crowding in our unit. LOS and NEC are both serious complications of prematurity associated with higher mortality and short- and long-term morbidities. In the prevention of NEC, efforts should be focused on promoting exclusive breastmilk feeds with mother's own milk and donor milk where possible.

As expected, severe IVH and cystic PVL were higher in weight categories <1001g. A study in Johannesburg had comparable rates of severe IVH (7% vs 5.8% in our centre) and lower rates of cystic PVL (0.9 % vs 2.4% in our centre)[29]. Severe IVH and cystic PVL is associated with adverse neurodevelopmental outcomes and increased risk of cerebral palsy. Identifying infants with severe IVH's and PVL is important to risk stratify infants for long term neurodevelopmental follow up.

The rate of CLD <33w was lower than that of the VON. One of the reasons attributable to this finding is due to the application of limitations of care to infants <27w and <800g where infants with significant respiratory compromise are less likely to survive.

Groote Schuur hospital is one of the better equipped government hospitals in Africa. It is important to compare the differences in outcomes of neonates in lower- and middle-income countries to higher income countries in order to highlight the discrepancies of available resources and to aim to improve on available resources in the context of LMICs. This information is invaluable in motivating for public health efforts, political commitment and in

implementing strategies aimed at preventing preterm deliveries and their care after birth. Furthermore, this data is paramount in the counselling of parents appropriately in terms of expectations of survival and morbidity in our setting. In the context of LMICs, it has been shown that relatively inexpensive measures can have a meaningful impact in improving survival of VLBW infants in poorly resourced settings. Important strategies include improved access to antenatal care, neonatal resuscitation training, prevention of mother to child transmission of HIV, and promotion of breastmilk and Kangaroo Mother care[21]. High impact strategies recommended by the WHO in 2015 include antenatal corticosteroids, CPAP and surfactant replacement therapy[30]. Importantly, utilising combined interventions are the most effective strategy in reducing neonatal mortality [31].

The goal of caring for preterm infants should be on improving morbidity free survival. Further efforts need to be focused on addressing the cost of morbidities on the health care system and the ability to support families in the long-term care of these infants, especially in the LMIC setting.

Strengths and limitations:

The large sample size and prospective data collection are strengths of this study. All records were audited and corrected at discharge, ensuring the quality of data captured. This is a single centre study and may not be generalizable to other resource limited settings. A limitation of our study is that weight categories were used instead of gestational age due to unsure dates and gestation of our population. In depth folder review of morbidities may have identified additional risk factors for each individual morbidity. Our center's membership in VON allows access to a large database with the ability to benchmark against hospitals around the world. Data obtained from this study enables our centre to identify and implement quality improvement interventions at GSH.

Conclusion:

The mortality rates of GSH VLBW infants are higher than those of VON, but with lower morbidity rates. The challenge remains in implementing sustainable and effective measures to shift mortality rates of our preterm infants within the constraints of our setting and resources.

The ultimate goal is to optimize morbidity free survival of our VLBW infants, especially in the context of limited resources, given the economic and psychosocial impact which morbidity has on families in caring for infants with complex health needs or neurodevelopmental impairment. Further research is needed in the long term follow up of infants with high-risk morbidities and long-term outcomes. Long term follow up of premature infants with high risk morbidities is important in our setting in order determine neurodevelopmental outcomes of these infants and to institute multidisciplinary input and rehabilitation timeously.

Ongoing audits and publication of our local mortality and morbidity data are important to update health protocols, create awareness, bolster political will, guide intervention and in counselling parents appropriately.

Note: Vermont Oxford Network played no role in the design, analysis, interpretation, or reporting of this research. The views, conclusions, and opinions expressed are solely those of the authors and do not represent Vermont Oxford Network. Unpublished data provided courtesy of Vermont Oxford Network.

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Appendix A: Vermont Oxford Network [18] Data Definitions

VON serves as a neutral, independent party in analyzing and providing benchmarking data for individual centers and groups that can be used to identify local opportunities for improvement of neonatal care.

Four databases collect information on very low birth weight infants, all patients cared for in a NICU, follow-up for extremely low birth weight infants, and infants cared for in resource-limited settings around the world (https://public.vtoxford.org/).

Necrotizing Enterocolitis (NEC)	The infant had Necrotizing Enterocolitis (NEC) diagnosed at surgery, at postmortem examination, or clinically and radiographically using the following criteria: At least <u>one</u> of the following clinical signs present: • Bilious gastric aspirate or emesis • Abdominal distension • Occult or gross blood in stool (no fissure) **And** At least <u>one</u> of the following radiographic findings present: • Pneumatosis intestinalis • Hepato-biliary gas • Pneumoperitoneum
Late Onset Infection	Indicates whether the infant has either Late Bacterial Infection and/or Coagulase Negative Staph and/or Fungal Infection after Day 3 of life. This is defined as confirmed culture of blood or CSF.
Severe Intraventricular Hemorrhage (IVH)	Indicates whether the infant has a grade 3 or 4 periventricular-intraventricular hemorrhage (PIH) on or before day 28 • Grade 3: Intraventricular blood, ventricular dilation • Grade 4: Intraparenchymal hemorrhage

Cystic Periventricular Leukomalacia	The infant has evidence of cystic periventricular leukomalacia on a cranial ultrasound, CT, or MRI scan obtained at any time. • To be considered cystic periventricular leukomalacia there must be multiple small periventricular cysts identified. • Periventricular echogenicity on ultrasound without cysts should not be coded as cystic periventricular leukomalacia. • A porencephalic cyst in the area of previously identified intraparenchymal hemorrhage should not be coded as cystic periventricular leukomalacia. • Periventricular abnormalities on CT or MRI should not be coded as cystic periventricular leukomalacia unless multiple small periventricular cysts are identified.
Pneumothorax	The infant had extrapleural air diagnosed by chest radiograph or needle aspiration (thoracentesis).
Severe Retinopathy of Prematurity (ROP)	Indicates whether the infant has a stage 3, 4 or 5 ROP • Stage 3: Presence of a ridge with extraretinal fibrovascular proliferation • Stage 4: Partial retinal detachment • Stage 5: Total retinal detachment
Chronic Lung disease (CLD) <33 weeks	Infants < 33 Weeks post menstrual age who are on oxygen. or If the infant is discharged home or transferred on or after 34 weeks and is on oxygen.