In-hospital neonatal mortality in a level-two hospital in Cape Town, South Africa

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GBRCIN002

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

Master of Medicine (MMed) – Paediatrics

Faculty of Health Sciences

University of Cape Town

Date of Submission: June 2022

Revisions submitted: October 2022

Supervisor: Dr David le Roux

Contents

Declaration

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

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Date: …2022/06/22…….

Acknowledgement

To Doctor David Le Roux for his invaluable assistance and supervision during my MMED journey. Thank you for the generous patience , guidance and expertise during this longer-than usual process. I appreciate your unwavering support and I am deeply indebted to you.

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22 June 2022

Postgraduate Committee

Faculty of Health Sciences

University of Cape Town

To Whom it may concern:

Re: MMed (Paediatrics) submission GBRCIN002

Included please find my MMed thesis. The study protocol, manuscript and

appendices are identified in the contents page.

The manuscript has been accepted for publication in the South African Journal of Child Health, a peer-reviewed academic journal.

I have attached a PDF version of the pre-publication manuscript as an appendix.

I trust this will meet with the approval of the committee.

Sincerely

Dr Cindi Gabriels

MBChB, DCH, FCPaed(SA),

Research Proposal: "In-hospital neonatal mortality in level-two hospital in Cape Town, South Africa: a retrospective study over a six-year period"

Dr Cindi Gabriels: Paediatric Registrar; MMed student, Department of Paediatrics and Child Health, University of Cape Town

Dr Dave le Roux: Principal Investigator and supervisor, Department of Paediatrics and Child and Health, University of Cape Town; and Department of Paediatrics, New Somerset Hospital

1) Summary

In 1990, through the Millennium Development Goals (MDG) the international community expressed their commitment to reducing under- five mortality by two thirds, between the period 1990 and 2015.[1,2] Whilst this was not achieved in its entirety, significant progress was made in child survival in most countries, including southern African countries, primarily as a result of interventions aimed at preventing those diseases associated with mortality outside of the neonatal period.[2-5] This included a primary focus on infectious diseases such as malaria, pneumonia and gastroenteritis, as well as vaccine preventable diseases.[1,2]

The top 5 causes of under-five mortality in South Africa include prematurity, asphyxia, HIV/AIDS, pneumonia and diarrhoeal diseases.[6,7] However, neonatal mortality remains a major public health challenge: the neonatal period is the most vulnerable time of life[1]**:** 47% of under-five mortality occurs in the first 28 days of life,[2] and decreases in neonatal mortality have been less dramatic than decreases in mortality in older children.[7] Thus for under-five mortality to decrease further, it is imperative to address the burden of neonatal mortality.[2] In 1990 the global under-five mortality rate (U5MR) was 91 per 1000 live births which reduced to 39 per 1000 live births in 2017.[2] In contrast the neonatal mortality rate (NMR) decreased from 37 per 1000 live births to 18 per 1000 live births in 2017.[2] In South Africa, the U5MR declined from 60 per 1000 live births in 1990 to 41 per 1000 live births in 2015,[6] but decreases in NMR have been less dramatic: NMR decreased from 16 per 1000 live births in 1998 to 14 per 1000 live births in 2008,[8] but since then has remained between 11 and 12 per 1000 live births up until 2015.[7]

Asphyxia, prematurity and neonatal sepsis are acknowledged as major causes of neonatal mortality;[1,7,9] however there is little data regarding the individual contribution of these to overall neonatal mortality. This project seeks to understand the causes of neonatal mortality in a level 2 hospital in Cape Town, South Africa.

2) Background

Understanding the causes of child mortality provide important public health insights. The Millennium Development Goals (MDGs) represented the world's commitment to reduce poverty and ill health.[10,11] The international community was committed to reducing the under-five mortality rate (U5MR) by 2/3 between 1990-2015.[2,10] MDG 4 was unfortunately not achieved and although the U5MR decreased by 1/3 in many parts of the world, from 91 per 1000 live births in 1990 to 43 per 1000 live births in 2015. Numerically it means that 12.7 million children under the age of five died in 1990, with 5.9 million children under the age of five dying in 2015.[2] This decrease was largely through interventions aimed at reducing deaths in the non-neonatal period, caused by infectious diseases (diarrhoea, pneumonia, malaria) and vaccine preventable diseases which are important causes of mortality after the neonatal period.[1,2]

However, over the past 3 decades, there has been a much smaller reduction in the neonatal mortality rate (NMR). Globally, the NMR decreased from 37 deaths per 1000 live births in 1990 to 18 per 1000 live births in 2017, and the number of neonatal deaths declined from 5.0 million to 2.5 million.[2] Of the estimated 5.4 million child deaths under five years in 2017, nearly 1 million occurred on the first day of life and close to three-quarters occurred in the first week of life.[2] Therefore an increasing proportion of the under-five child deaths now occur in the neonatal period. If the current trend continues, an estimated half of the 56 million child deaths between 2018-2030 will occur in the neonatal period,[2] making neonatal deaths a major public health priority.

The "Mother-Baby Package" was published by the World Health Organisation (WHO) in 1996, which emphasized the mother baby dyad, and it was assumed that what was beneficial for the mother would be beneficial for the baby.[12] Basic interventions addressing neonatal complications were the main focus, but little attention was given to neonatal mortality by the public health community, the maternal health and child health communities. In 2005, the world's attention was caught by the "Neonatal survival Series: 4 million neonatal deaths: When? Where? Why?" by Lawn et al.[1] The series showed that neonatal deaths, as a proportion of total under-five deaths, were increasing. The following points were highlighted:

a) When are babies dying?

An estimated three- quarters of neonates die within the first week of life and the first day of life carries the highest risk of mortality, resulting in nearly half of neonatal deaths (25-45%).[1]

b) Where are babies dying?

Approximately 98-99% of deaths occur in low and middle income countries (LMIC), and more than half of neonates die at home; yet most research focuses on the 1% of deaths in high income countries.[1] Therefore more research and data in LMIC is needed. As Lawn et al declared, "The communities with the most neonatal deaths have the least information on these deaths and the least access to cost-effective interventions to prevent them."[1] A NMR < 15 per 1000 live births is considered a low mortality rate and a NMR > 45 per 1000 livebirths is considered to be high rate.[1] South Africa has a NMR of 11-12 per 1000 livebirths,[2] but there is substantial regional variation, especially in rural areas.[6,9]

c) Why are babies dying?

More than 80% of neonatal deaths are due to preventable or treatable conditions: preterm birth and its complications (35%); severe infections (15%); asphyxia (24%); and congenital abnormalities (9%).[13] Associated risk factors highlighted by Lawn et al showed that low birth weight is an important indirect cause of death. Maternal obstetric complications and poverty are strongly associated with an increased risk of neonatal mortality. There is also geographic variation in the severity of these factors: neonates have an 11 fold greater risk of dying due to severe infections and an 8 fold risk of dying due to asphyxia in a low to middle income country (very high-mortality country) in comparison to a high income country (low-mortality country).[1] Almost 50% of deaths are due to infection in very high neonatal mortality settings (NMR >45), but in low mortality settings (NMR <15), only 20% of deaths are caused by pneumonia or sepsis.[1]

Lawn et al made quite a powerful statement: "Preventing deaths in newborn babies has not been a focus of child survival or safe motherhood programs. While we neglect these challenges, 450 newborn children die every hour, mainly from preventable causes, which is unconscionable in the 21st century."[1] The MDGs did not focus on neonatal deaths;[1,5] the Sustainable Developmental Goals (SDGs) are an attempt to change that, and place neonates on the post-2015 global agenda.[11] [14] The SDG 3 target for 2030 is a global NMR of 12 deaths per 1000 live births.[1,6,11]

There has been good progress since the 2005 Lancet "Neonatal survival" series. The emphasis on newborn health has been shifted from being invisible in the 1990's to being central on the global health agenda. The "Every Newborn Series" in the Lancet in 2014 identified various opportunities and challenges in integrating the neonatal and maternal health communities. Darmstadt et al identified target areas: ending preventable neonatal deaths and stillbirths, ending preventable child and maternal deaths, as well as focusing on sexual and reproductive health in females.[15] In addition,

it was recommended that countries should take ownership and individualize, prioritise and design programmes and define their own goals.[16] The "Every Newborn Action Plan" (ENAP), launched in 2014, proposed strengthening the neonatal focus within maternal, child and reproductive health.[7,14,16,17]

As neonatal survival has started to receive greater acknowledgement internationally, in our local context, South Africa has also adopted several neonatal survival strategies. The National Perinatal Morbidity and Mortality Committee (NaPeMMCo) Reports, based on the Lancet Neonatal Survival Series,[18,19] identify cost-effective high-impact interventions in South Africa: resuscitation, immediate assessment and stimulation, early exclusive breastfeeding, immediate thermal care, clean birthing areas, handwashing with soap, Kangaroo Mother Care (KMC) and full facility care e.g. nasal Continuous Positive Airway Pressure (nCPAP).[7,20] NaPeMMCo has intervened by enrolling strategic neonatal care training programs currently in South Africa . These include:

1) ESMOE (Essential Steps in the Management of Obstetric Emergencies) enrolled in 2011[7]
2) HBB (Helping Babies Breathe) implemented in July 2012[7,21]
3) HHAPINESS (Health system improvement, Health care providing training, reducing deaths due to Asphyxia, reduce deaths due Prematurity, reduce deaths due to Infection and an Incorporated Neonatal Survival Strategy.[22 7]
4) PEP (Perinatal Education Programme) for training nurses in South Africa.[9,23]
5) Management of Sick and Small Newborn in Hospital (MSSN) was launched in September 2014 and targeted preterm births and asphyxiated neonates. This entails a comprehensive care chart and easily understandable information for healthcare providers. It covers basic care (cleanliness with regards to handwashing and cord care), warmth, adequate nutrition, intravenous fluids and antibiotics, oxygen, care for asphyxiated babies and their assessment and provides important drug dosages.[24 7]
6) First Thousand Days: This promotes maternal and neonatal health from the beginning of pregnancy up until the age of two years. The aim is to decrease neonatal and child mortality and improve developmental outcomes.[25]

The three interventions HBB, MSSN and nCPAP, of the fifteen according to PRICELESS SA (Priority Cost Effective Lessons for Systems Strengthening South Africa) , if rolled out at scale could result in an achievable NMR by 2030 as per SDG 3.[7]

There has been some research into the cause of neonatal deaths in South Africa, and potential interventions. In a retrospective database review of 142 hospitals between October 1999 and

September 2003, Velaphi et al described 4502 neonatal deaths. Prematurity accounted for 35.2 % of deaths and 32% of deaths were due to asphyxia-hypoxia. Of all the deaths due to asphyxia-hypoxia, intrapartum asphyxia was identified as the main obstetric cause of death. Inadequate fetal monitoring was the main avoidable factor.[26] In a review of very low birth weight infants over 3 years from a single institution, the same authors described a 72% survival to discharge rate, with higher mortality among neonates born less than 1000 g. Prematurity accounted for 63% of deaths. The overall survival to discharge rate for extremely low birthweight neonates was 32 % versus 84 % survival to discharge rate for very low birth weight neonates.[27]

Modifiable factors impacting on neonatal survival were collected for 102 sites in South Africa; they included inadequate staffing and facilities, poor care in labour, poor neonatal resuscitation and basic care, and difficulties for patients in accessing health care. Pattinson et al concluded that effective, practical and affordable measures must be undertaken to reduce the NMR.[23] Kirsten et al showed in a tertiary hospital that early non-invasive respiratory support with nCPAP in extremely low birth weight infants (ELBW) and the administration of exogenous surfactant showed similar results in comparison to developed countries.[28] In another tertiary hospital, Pieper et al showed that the use of pressure support in the form of nCPAP in extremely low birthweight preterm neonates, not meeting criteria for neonatal intensive care unit admission , reduced mortality by 50% compared to those who received oxygen alone. With nCPAP the survival rate increased by 125%. The use of nCPAP increased the survival of small babies who, prior to nCPAP, had a dismal outcome.[29] Both these studies were done at tertiary facilities. The early initiation of nCPAP versus late initiation of nCPAP reduced the need for invasive mechanical ventilation by 45% according to a Cochrane review article.[30]

The South African government is committed to reduce the U5MR as to meet the targets set by the Sustainable Developmental Goals, namely an U5MR less than 25 and a NMR less than 12 by 2030.[6,11] However, on a subnational level, the quality , accuracy and completeness of the data collected show many discrepancies as they are collected by different systems . There is need to improve the quality and accuracy of existing databases.[6,9] Furthermore, most of the South African research has been done at tertiary academic neonatal units, and very little research has been directed at the level 2 or regional hospitals. Thus we resolved to review the neonatal mortality at the New Somerset Hospital Neonatal Unit, to determine the neonatal mortality rate, main causes and possible preventable factors.

3) Rationale & objectives for the study

1) How many in-hospital neonatal deaths (deaths within the first 28 days of life) occurred in the neonatal unit at New Somerset hospital between 01/01/2011- 31/12/2018;
2) What is the in-hospital Neonatal Mortality Rate (NMR) (the number of babies under 28 days who die in a year, per 1000 live births in the same year) for each year and to establish a trend.
3) What are the main causes of death? Early Neonatal Death (ENND) vs Late Neonatal Death.
4) What is the impact of gestational age and birth weight on mortality?

4) Methods

A database of neonatal in-hospital deaths occurring in the neonatal unit in the New Somerset Hospital has been maintained by the neonatal consultants working in the neonatal unit. We propose to review the neonatal deaths captured in the database.

Study design: Retrospective description of an existing database of all neonates admitted to the neonatal unit between 1 January 2011 and 31 December 2018 and who died within the first 28 days of life in hospital. This includes all, inborn or outborn, including transfers to the unit who died within the first 28 days of life in hospital will be included in the study. For calculation of the Neonatal Mortality Rate, only the inborns babies will be used.
(New Somerset Hospital Neonatal Medicine Database; HREC REF Number: 391/2011)

Recruitment and enrolment: No participants will be actively recruited as the dataset is already established and data already collected

Institutional approval will be obtained before commencement of the study.

Research procedures and data collection methods: The investigators will analyse the existing database. The data has been collected by the neonatal consultants and is being maintained by the medical staff in the neonatal unit. Details of all babies who died within the neonatal period in the neonatal unit are entered into a file in the ICU and PPIP data system. The details are entered weekly into an Excel spreadsheet.

Details include: age of baby, gender, mode of delivery, single or multiple pregnancy, gestation, weight, HIV exposure and status, syphilis exposure, cause of death, inborn or outborn and modifiable and avoidable factors. Some other risk factors, including maternal infections, were also captured.

Database patient folders will not be retrieved, nor will each case be interrogated regarding possible adverse outcomes. For the purpose of this review we will accept the clinical judgement of the attending clinician at the time the death was entered into the database

Data and safety monitoring: The database is held in a password-protected folder; only the head of the unit has access to the database. Once ethics approval has been granted, I will receive an anonymous de-identified subset of the data without any personal identifiers.

Data analyses: Data will be analysed in Excel. Frequency tables, histograms and basic analyses will be drawn from the main database. Dr le Roux will assist with data analysis.

Limitations: As this is a retrospective analysis of an existing database, and detailed folder reviews are not anticipated, the analysis at this stage will be limited to data that were captured at the time the event was recorded.

5) Description of risks and benefits

As this is a retrospective description of an existing database and no participants will be actively enrolled; there are no additional risks or benefits for the study participants.

6) Informed consent process

Not applicable.

7) Privacy and confidentiality

Confidentiality for individual patients is assured once the data is cleaned, as all personal identifiers will be removed from the database; the final analytical version will be completely anonymized.

8) Reimbursement for participation

Not applicable.

9) Emergency care and insurance for research-related injuries

Not applicable.

10) What happens at the end of the study?

Not applicable

11) Dissemination

This will form the basis of an MMed degree. The final manuscript will be published in a local peer reviewed journal. Dr le Roux will advise on journal selection and publication process. The data will remain the property of Dr le Roux.

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Abstract

Background

Neonatal mortality (deaths in the first 28 days of life) is a major contributor to under-5 mortality in South Africa. Many advances in neonatal care have been introduced, but the impact of these interventions has not been studied outside of tertiary academic centers.

Objectives

To describe neonatal mortality in the neonatal high care unit at New Somerset Hospital in Cape Town, South Africa, over an 8 year period.

Methods

Neonatal deaths were captured and entered into a database; deaths were coded according to Perinatal Problem Identification Program categories.

Results

Neonatal deaths from 2011 to 2018 were analyzed, excluding 2014. There were 296 neonatal deaths; median birthweight of neonatal deaths was 1140g (interquartile range (IQR) 790 – 2420g); median gestation was 29 weeks (IQR 25 – 38). Immaturity (132/296, 45%) was the most common cause of death, followed by hypoxia (67/296, 23%) and infections (61/296, 21%). There were 250 (84%) neonatal deaths in the first week of life; there was a trend towards decreasing number of neonatal deaths (from 48 in 2011 to 34 in 2018), and rate of deaths (from 45.2 per 1000 admissions to 28.2 per 1000 admissions). This was driven by decreased deaths due to immaturity; number of deaths due to other causes remained approximately constant.

Conclusions

We observed decreasing number of neonatal deaths and rate of deaths per 1000 admissions, with the largest decrease due to prematurity. Advances in respiratory care for preterm neonates may have contributed to decreased mortality due to immaturity. Upstream obstetric interventions will be required to address hypoxia-related causes of neonatal mortality.

In-hospital neonatal mortality in a level-two hospital in Cape Town, South Africa

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Introduction

In 1990, through the Millennium Development Goals (MDG's), the international community expressed their commitment to reduce the under-5 mortality by two thirds, between 1990-2015.[1]

Neonatal mortality (deaths in the first 28 days of life) has been a major contributor to under-5 mortality in South Africa, accounting for a third of under-5 deaths in 2015.[2] Due to improvements in management of HIV, pneumonia and gastroenteritis,[3] under-5 child mortality in South Africa decreased dramatically over the last 20 years, from a peak of 80 deaths per 1000 live births at the height of the HIV epidemic in 2004[4] to 34 deaths per 1000 live births in 2018.[3] However, neonatal mortality in South Africa has remained static at 11-12 deaths per 1000 live births for nearly 20 years,[3,4] so the relative contribution of neonatal mortality to total under-5 mortality has increased from 14% in 2002 to 32% in 2018.[3]

Understanding the causes of under-5 child mortality is crucial and provides important public and societal health insights in achieving the global goal by 2030.[1]

Neonatal mortality must be addressed if South Africa is to meet target 3.2.1 of the Sustainable Development Goals (SDG's) by 2030, namely under-5 child mortality of less than 25 deaths per 1000 live births.[1]

The leading causes of under-5 mortality in South Africa are prematurity, asphyxia, HIV/AIDS, pneumonia and diarrhoeal diseases;[2,4] neonatal sepsis is also a major contributor to both early (day 1-7) and late (day 8-28) neonatal deaths.[5] In comparison to most countries in Africa and Asia; where less than 25 % of deaths are registered, South Africa has access to reliable data sources.[3,5] Much research into the cause of neonatal deaths in South Africa and potential modifiable factors has been performed.[6]

Most pooled neonatal death surveys focus on causes of early neonatal deaths (ENND's) and late neonatal deaths (LNND's) are under-reported.[7,8] In a retrospective database review of 142 hospitals between October 1999 and September 2003, Velaphi et al described 4502 neonatal deaths. Prematurity accounted for 35% of deaths and 32% of deaths were due to asphyxia-hypoxia.[9] Early continuous positive airway pressure (CPAP)[10] and exogenous surfactant therapy[11] has improved survival of extremely low birth weight neonates (ELBW) in tertiary neonatal units. High flow nasal cannula oxygen (HFNC) has been used for pre-term neonates instead of CPAP with good results.[12] Furthermore, there

is evidence that outborn neonates transferred to tertiary neonatal centers have worse outcomes than inborn neonates.[13] However there is minimal evidence regarding impacts of these recent improvements in neonatal care on neonatal mortality outside of tertiary academic centers; nor of outcomes of outborn neonates who are transferred to non-tertiary neonatal units, where most neonatal care in South Africa is delivered.[6]

For these reasons, we aimed to investigate neonatal mortality in a level 2 neonatal unit in Cape Town, South Africa, to better understand causes of early and late neonatal mortality; and to analyze inborn vs outborn neonatal mortality.

Methods

New Somerset Hospital (NSH) is a level 2 hospital in Cape Town, South Africa. NSH performs about 6000 deliveries per year, and receives referrals from a wide geographic area, including local urban primary level delivery facilities, and remote rural hospitals up to 200 km away.

CPAP, surfactant and short-term ventilation (<3 days) are offered; high flow nasal cannula oxygen (HFNC) was introduced in 2015, but long-term ventilation (3 days or more), high-frequency oscillatory ventilation (HFOV), inotropic support, total parenteral nutrition are not available.[14] Neonates who require escalation of neonatal care are referred to the tertiary hospital, Groote Schuur Hospital (GSH); neonates requiring surgical intervention are referred to Red Cross War Memorial Children's Hospital (RCWMCH).
Neonates born at other facilities and transferred to NSH were considered "outborn".

A database of all neonatal deaths was maintained by the lead consultant in the neonatal unit. Approval to maintain the database was obtained from University of Cape Town (UCT) Human Research Ethics Committee (HREC Ref 391/2011). The neonatal mortality database included all neonates who died either on-site at New Somerset Hospital, or after transfer to a level 3 facility (GSH or RCWMCH); information about neonatal deaths was captured in real time by doctors (registrars and medical officers) into a file kept in the neonatal high care unit (HCU), and entered into a password-protected database (initially an Excel spreadsheet, then an Access database) by the neonatal consultant on a weekly basis. Variables included gestational age, weight, sex, mode of delivery, and HIV exposure status. Early neonatal deaths were submitted to the local coordinators of the Perinatal Problem Identification Program (PPIP), a structured national project for district-level

longitudinal tracking of still births and early neonatal deaths.[5] Deaths were coded according to categories used by the PPIP for main causes of death (immaturity, hypoxia, sepsis, congenital anomalies and other). Birth weight was considered in the following categories: >=2500g, 1500-2499g, 1000-1499g and <1000g. Survival status of neonates after transfer to level 3 was determined and entered monthly. An anonymous de-identified subset of data without any personal identifiers was analyzed by the investigators. This analysis was restricted to in-hospital deaths occurring in the first 28 days of life. Neonatal deaths that occurred in labour ward were excluded, as they were never admitted to the neonatal unit. Neonates who were discharged and died within 28 days of birth at home or in other hospitals were not included. The study was approved by UCT Human Research Ethics Committee (HREC REF 71/2019). Permission to conduct the study was granted by the chief executive officer of NSH.

Statistical analysis

Categorical variables were compared as percentages and proportions, and by chi-squared test; means were compared by t-test. Continuous variables were presented as median and interquartile range (IQR) as they were not normally distributed, and compared with Mann-Whitney U test. Frequency tables, histograms and basic analyses were generated in Microsoft Excel; medians and IQR were calculated in Stata version 16.

Results

Neonatal deaths from 2011 to 2018 were compiled, with the exclusion of 2014, due to incomplete data capturing for several months of that year, supplementary table 1. In the seven years under review, there were 46 441 births at NSH, and 8166 admissions to the neonatal unit: 6205 (76%) of the neonatal admissions were inborn and 1961 (24%) were transferred in from other birth units. There were 296 neonatal deaths associated with NSH high care unit (HCU) ; 219 (74%) were inborn and 77 (26%) were outborn, either born before arrival or transferred in from a level one facility or maternal obstetric unit, table 1. Most, (221, 75%) , of the neonatal deaths occurred at NSH, but 75 (25%) occurred after transfer to another unit. There were 171 (58%) males. Median birthweight was 1140g (IQR 790 – 2420); nearly half the neonatal deaths (130, 44%) had birth weight <1000g. Median gestation of neonates who died was 29 weeks (IQR 25 – 38), with no significant difference between inborn and outborn (p=0.86). Overall, a majority of neonates (181/296, 61%) who died were delivered by normal vertex delivery (NVD) and were not

HIV exposed (220/296, 74%). Median age at death was day 1 (IQR 1-4) for outborn vs day 2 (IQR 1-4) for inborn, p=0.20.

"Immaturity" was the most commonly coded cause of death (132/296, 45%); this category included neonates who had been recorded as having extreme prematurity (94, 32%), hyaline membrane disease (31, 11%) and pre-term intraventricular haemorrhage (7, 2%). "Perinatal hypoxia" included hypoxic ischaemic encephalopathy (32, 11%) and meconium aspiration syndrome (MAS) with or without persistent pulmonary hypertension of the newborn (PPHN) (25, 8%). Perinatal hypoxia was a more common cause of death among inborn neonates (54/219, 25%) compared to outborn neonates (13/77, 17%), but this difference was not statistically significant, p=0.16.

Infection-related causes included 19 cases (6%) of necrotizing enterocolitis (NEC), 2 of which had an organism identified (one each of *Serratia marcescens* and *Escherischia coli*) and 17 were culture-negative. There were 38 neonatal deaths due to non-abdominal sepsis; 31/38 (82%) were culture-negative; those with positive cultures included 3 cases of *Pseudomonas aeruginosa*, and one case of each of *Streptococcus agalactiae, Candida albicans*, *Enterobacter cloacae*, and a mixed infection of *Klebsiella pneumoniae* and *Acinetobacter baumanii*. There were four (1%) neonatal deaths due to congenital syphilis. Infection-related causes of death were more common among outborn neonates (25/77, 32%) vs inborn neonates (36/219, 16%, p=0.003), Supplementary table 2.
Of the 30 neonates dying with congenital abnormalities, there were four with trisomy 18; 12 had multiple anomalies but not a recognizable syndrome; seven had congenital cardiac lesions, two of whom also had trisomy 21; five had pulmonary hypoplasia, and one each with a central nervous system lesion and congenital anaemia. The category of "other" causes of death included four neonates who had haemorrhages (one subaponeurotic, one intracerebral, two other exsanguinating haemorrhages) and two due to metabolic disorders.

Among neonates of different birth weight categories, there were differences in method of delivery and cause of death: most ELBW neonatal deaths (107/130, 82%) followed NVD, and immaturity was the main cause of death (104/130, 80%); whereas neonatal deaths with birth weight >2500, hypoxia was the main cause (50/72, 69%) and Caesarean section was the most common delivery method (39/72, 54%), table 1. There were no significant

differences in age at death among neonates of different birth weight categories.

Throughout the study period, antenatal HIV prevalence among pregnant women remained constant at about 20%; there were similar numbers of deaths of HIV-exposed neonates in all weight categories, table 1. There was a higher proportion of HIV exposed neonates dying due to infectious causes (26/61, 43%) compared to other causes (50/235, 21%, p=0.001), Supplementary fig 1.

There was a gradual trend towards decreasing number of neonatal deaths (from 48 in 2011 to 34 in 2018) and rate of deaths (from 45.2 per 1000 admissions to 28.2 per 1000 admissions, table 2). This was largely driven by decreased deaths due to immaturity, from 27 (56%) in 2011 to 15 (44%) in 2018, figure 1; deaths among ELBW decreased from 25 (52%) to 12 (35%), table 2. Number of deaths in other birth weight categories and due to other causal categories remained approximately constant, table 2. Mean number of deaths due to immaturity before 2014 (average 25.3 per year) was significantly less than mean number of deaths after 2014 (average 14.0 per year, p=0.01). The decrease in number of deaths due to immaturity was more marked in neonates who were inborn (from 21 in 2011 to 11 in 2018) compared to those who were outborn (from six to four), supplementary figure 2. There were four deaths due to congenital syphilis prior to 2015 and none after 2015. Age at death after 2015 was lower (median 1 day, IQR 1 – 5) compared to neonates born before 2015 (median 2 days, IQR 1 – 4), supplementary figure 3; but this was not statistically significant, p=0.86.

Discussion

In this retrospective observational study, we observed decreasing numbers of neonatal deaths and decreased in-hospital neonatal mortality among both inborn and outborn neonates; the decrease in number of deaths was more marked for deaths due to immaturity than for other cause of death codes. Over the same period of time, neonatal mortality rate in South Africa remained almost unchanged (between 11 and 12 deaths per 1000 live births[3]; in Cape Town (Metro West), early neonatal deaths decreased from 7.6 to 6.4 deaths per 1000 live births.(New Somerset Hospital 2018 PPIP report, Dr Lizel Jacobs, personal communication).

Possible reasons for the observed decrease in neonatal deaths due to immaturity and in

neonates in the lowest birth weight category through the course of the study period may be due to changes in policy regarding respiratory support for preterm neonates. Prior to 2015, neonates needing respiratory support received low-flow, non-humidified, blended oxygen. Limited CPAP machines were available for neonates weighing >1000g and if gestation was at least 28 weeks. From 2015, warmed humified blended high flow nasal cannula oxygen was available for all neonates, irrespective of weight or gestational age. From 2017, CPAP and surfactant were made available to neonates with birth weight >800g if gestational age was at least 28 weeks.[14]

High flow nasal cannula (HFNC) oxygen therapy in preterm infants has been associated with similar outcomes to nasal continuous airway pressure (CPAP) with fewer complications and less nasal trauma.[15] It is possible that the introduction of early HFNC in 2015 was associated with improved survival of preterm inborn neonates. The reason that deaths of outborn preterm neonates did not decrease to the same extent as inborn preterm neonates may be due to delays in transport from other facilities; neonates may have spent many hours receiving unheated non-humidified oxygen before admission to NSH, which may have caused hypothermia, atelectasis and lung inflammation.[13] Outborn neonates were also more likely to die of infectious-related causes: it is possible that potential improvements in respiratory care were mitigated by ongoing high risk of exposure to infection while in transit to NSH. It is difficult to see from this data whether decreasing the threshold to qualify for CPAP and surfactant in 2017 had any further impact on neonatal mortality. Improvements and advances in the care of ELBW, (as per "Standard post-natal interventions for peri-viable preterm birth in extremely low birth weight infants in the Western Cape Province Department of Health"),[14] has improved the survival of these premature babies.

There had been some concern that introduction of HFNC in 2015 may prolong survival of ELBW neonates beyond day 7, but that most of these neonates would subsequently die of sepsis (nosocomial) or NEC.[16] Kirsten et al. described the survival of ELBW neonates in a tertiary center, Tygerberg Hospital, in Cape Town. A total of 318 inborn ELBW (500g-1000g)neonates were treated with CPAP and InSurE (intubation, surfactant and extubation). Despite showing a survival of 87 % on day 7, only 75 % of neonates survived until discharge. Causes of death were attributed to sepsis and NEC in 37 neonates after day 7.[11] However, we did not observe an increase in late deaths from other causes, and the age at death did not change throughout the study period . We believe that the observed decrease in early

deaths due to immaturity is real, and is not simply due to shifting the mortality burden into a different category.

There was minimal turnover in doctors working in the unit, but there was lower turnover of nursing staff; there were no other major changes in practice or policy regarding management of perinatal hypoxia, suspected sepsis or other neonatal conditions during the period under review.

The number of deaths due to hypoxia did not change much over the study period. Throughout the study period, NSH neonatal unit practiced therapeutic hypothermia for moderate / severe hypoxic ischaemic encephalopathy, and used amplitude-integrated electroencephalograms to monitor cerebral function in neonates with brain injury. However, addressing deaths due to perinatal hypoxia will require obstetric interventions and labour ward management; improved neonatal care will not be sufficient to substantially reduce hypoxia-related deaths.[17] There were relatively more deaths due to hypoxia among inborn neonates compared to those referred in from other facilities. It is possible that the most severely brain injured neonates who were born at other facilities demised within a few hours of life, before the ambulance transport could bring them to NSH.[9]

Improvements in obstetric care in identifying high risk deliveries (fetal distress; asphyxia) and transferring these babies in-utero to NSH, could possibly contribute to the increase in asphyxia-related in-born deaths. Local[13] and international studies have shown that in-utero transfer vs postnatal transfer to a higher level facility in anticipated high risk deliveries, improves neonatal outcome.[18,19] On the contrary, poor in-hospital obstetric care could also possibly contribute to the high burden of inborn asphyxia-related in-hospital deaths.[9]

The striking decrease in hospital-related neonatal deaths has not been seen in the annual PPIP reports. There are a number of reasons for this. PPIP reports early NND's according to the delivery unit, and includes all neonates who die in labour ward or after admission to a neonatal unit.[5] In this analysis, as we were only considering in-hospital mortality of the neonatal unit, we excluded all labour-ward deaths, but we included outborn neonates who were admitted to our unit if they subsequently died. For this reason, PPIP stats are a more sensitive longitudinal indicator of trends for delivery units and labour wards; the current analysis is better suited to detect trends in survival that are affected by changes in local

neonatal practice, not labour ward management.

There was a low rate of blood culture positivity among neonates who were attributed an "infection-related" cause of death. Although the unit policy is to always draw a blood culture before starting or escalating antibiotics, it is possible that some critically ill neonates may have died before cultures could be drawn, or that inadequate blood volumes were drawn,[20] and this resulted in low culture positivity; or that true pathogen growth was masked by skin contaminants.[21]

It is also possible that some of neonatal deaths labelled as "infection-related" may have been misclassified: neonates who had a clinical deterioration and demised may actually have had underlying cardiac or metabolic disease that was not diagnosed. Diagnosing sepsis in an ill neonate is often challenging because of the subtle, non-specific presentation and absence of optimal diagnostic tests . Clinicians are therefore obligated to treat all neonates with empiric antibiotics due to the high burden of suspected sepsis.[22] Sepsis, congenital cardiac conditions[23] and inborn errors of metabolism may have a similar clinical presentation.[24,25] Therefore , it is possible that these conditions may have been mislabeled as sepsis. However, other studies have shown that sepsis is often under-reported. In developing countries the majority of neonatal sepsis cases remain unproven. In a tertiary hospital in Soweto, South Africa, Mahdi, et al. conducted a prospective observational study and enrolled and reviewed 153 neonatal deaths. They observed that sepsis-related deaths might be under-reported and erroneously coded as immaturity-related causes.[26] This could possibly also contribute to the higher number of immaturity- vs sepsis-related coded deaths in our cohort.

There is good evidence that both HIV-infected and HIV-exposed uninfected (HEU) infants have higher rates of infectious morbidity than HIV-unexposed infants.[27,28] However the higher proportion of infection-related deaths among HIV-exposed neonates is difficult to interpret, as most neonates did not have nucleic-acid testing at the time of death. Universal antiretroviral therapy for pregnant women for prevention of mother to child transmission of HIV (PMTCT) was introduced in 2013[29] but universal birth PCR testing was only introduced in 2015;[30] it is possible that some considered to be "HIV exposed" were actually *in utero* HIV infected, and already had profound immune compromise at the time of death.

There are a number of important limitations with this data analysis. This was a

retrospective review of an existing database, therefore no patient folders were reviewed or interrogated regarding possible adverse outcomes. We accepted the clinical judgement of the attending clinician at the time the data were captured regarding the likely cause and category of death. However, misclassification of causes of death is possible, as very few autopsies were performed. As mentioned above, cardiac or metabolic diseases may have been misclassified as "infection-related" deaths.

Annual total numbers of births in labour ward and admissions to the neonatal unit were available; however as this was not disaggregated by birth weight categories, it is not possible to calculate a neonatal mortality rate per birth weight category as the denominator for each birth weight category is not known. It would have been valuable to calculate early and late neonatal death rates by weight category, to observe if any changes occurred during the period under review. The statistical and comparative analysis would have been more accurate if the denominator data regarding the admissions were captured.
Maternal antenatal corticosteroid administration prior to preterm delivery (between 26 weeks 0 days and 33 weeks 6 days gestation), has a profound impact on neonatal survival. According to a review article by Naidoo et aI studies have shown that a single course of antenatal maternal corticosteroids reduces incidence of respiratory distress syndrome by 34 % (RR 0.66, 95% CI 0.57-0.77) and reduces mortality by 31 % (RR 0.69, 95% CI 0.59-0.81)[31] Furthermore Naidoo et al et al report: a reduction in the incidence of intraventricular hemorrhage by 45% (RR 0.55, 95% CI 0.43-0.69) and necrotizing enterocolitis by 50 % (RR 0.50; 95% CI 0.32-0.78), the need for invasive ventilation by 32 % (RR 0.68; 95% CI 0.56-0.84) and early onset neonatal sepsis by 40 % [RR 0.60; 95 % CI 0.41-0.88).[6,31]

In a systematic review Lassi et al.,described several evidence-based and effective life-saving interventions: maternal antenatal corticostereoids prior to preterm labour, early initiation of breastfeeding, hygienic cord care, Kangeroo Mother Care for preterm infants and antenatal care.[32] The data on the impact of these interventions were not captured, hence it could not be described.

Data collection in 2014 was obviously incomplete: for 11 months of that year the number of deaths were far below the mean number of deaths for the rest of the study period, and there were three months with no deaths recorded at all. It would have been inappropriate

to include that year. However it is possible that some deaths were missed and not entered into the database: the same paediatrician supervised the unit from the end of 2014 till 2018, and the same data capture systems were in place; but with a manual system of data capture and data entry, it is possible that some deaths may have been missed. PPIP does not capture access to neonatal therapies (HFNC, CPAP, surfactant, therapeutic hypothermia): it was not possible to compare impact of neonatal therapies within the neonatal unit over time as this data was not available.

Conclusion

In this retrospective analysis of an existing database, we observed decreasing number of neonatal deaths over the period 2011-2018; the category with the largest decrease was inborn deaths due to prematurity, while all other numbers of deaths due to all other causes remained approximately the same. This period coincided with the introduction of high flow nasal cannula oxygen into the neonatal unit, and subsequent expansion of CPAP eligibility criteria from 1000g to 800g. These advances in respiratory support may have contributed to some of the observed decreased deaths due to prematurity.

Combinations of interventions may be required to reduce the residual burden of neonatal mortality in South Africa. Expansion of access to HFNC and CPAP may reduce deaths due to prematurity, but other upstream interventions, including improved access to antenatal care (for example antenatal corticosteroids for preterm labour) and other obstetric interventions in labour ward, will be required to address the residual burden of immaturity- and hypoxia-related causes of neonatal mortality.

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Neonatal mortality_tables and figures

Table 1: Characteristics of neonatal deaths by birth weight category

	Birthweight <1000g N=130	Birthweight 1000-1499g N=45	Birthweight 1500-2499g N=49	Birthweight ≥2500 N=72	Total N=296
Place born:					
Inborn	97 (75%)	31 (69%)	36 (73%)	55 (76%)	219 (74%)
BBA	14 (11%)	7 (16%)	3 (6%)	4 (6%)	28 (9%)
Vanguard MOU	6 (5%)	2 (4%)	5 (10%)	4 (6%)	17 (6%)
Vredenburg Hospital	6 (5%)	1 (2%)	2 (4%)	6 (7%)	14 (5%)
Wesfleur Hospital	4 (3%)	2 (4%)	0	2 (3%)	8 (3%)
Other	3 (2%)	2 (4%)	3 (6%)	2 (3%)	10 (3%)
Place died					
NSH	127 (98%)	25 (55%)	28 (57%)	41 (57%)	221 (75%)
RCWMCH	0	3 (7%)	6 (12%)	2 (3%)	11 (4%)
GSH	3 (2%)	16 (36%)	14 (29%)	29 (40%)	62 (21%)
Other	0	1 (2%)	1 (2%)	0	1 (0.7%)
Male sex	78 (60%)	25 (56%)	28 (57%)	40 (56%)	171 (58%)
HIV exposure status					
Unexposed	97 (75%)	31 (69%)	36 (73%)	36 (73%)	220 (74%)
Exposed	33 (25%)	14 (31%)	13 (27%)	16 (22%)	76 (26%)
Delivery method					
Normal vertex delivery	107 (82%)	20 (44%)	26 (53%)	28 (39%)	181 (61%)
Caesarean section	11 (8%)	23 (51%)	21 (43%)	39 (54%)	94 (32%)
Vaginal breech	12 (9%)	2 (4%)	1 (2%)	1 (1%)	16 (5%)
Forceps	0	0	0	4 (6%)	4 (1%)
Vacuum	0	0	1 (2%)	0	1 (0.3%)
Cause of death by PPIP category					
Immaturity	104 (80%)	24 (53)	4 (8%)	0	132 (45%)
Hypoxia	0	4 (9%)	13 (27%)	50 (69%)	67 (23%)
Infection	25 (19%)	15 (33%)	14 (29%)	7 (10%)	61 (21%)
Congenital anomaly	1 (1%)	2 (4%)	17 (35%)	10 (14%)	30 (10%)
Other	0	0	1 (2%)	5 (7%)	6 (2%)
Age at death, days: median (IQR)	1 (0 – 4)	2 (1 – 6)	2 (1 – 5)	2 (1 – 3)	1 (1 – 4)
Neonatal death category					
Early NND	108 (83%)	35 (78%)	41 (84%)	66 (92%)	250 (84%)
Late NND	22 (17%)	10 (22%)	8 (16%)	6 (8%)	46 (17%)

BBA: Born before arrival
MOU: Midwife obstetric unit
NSH: New Somerset Hospital
GSH: Groote Schuur Hospital

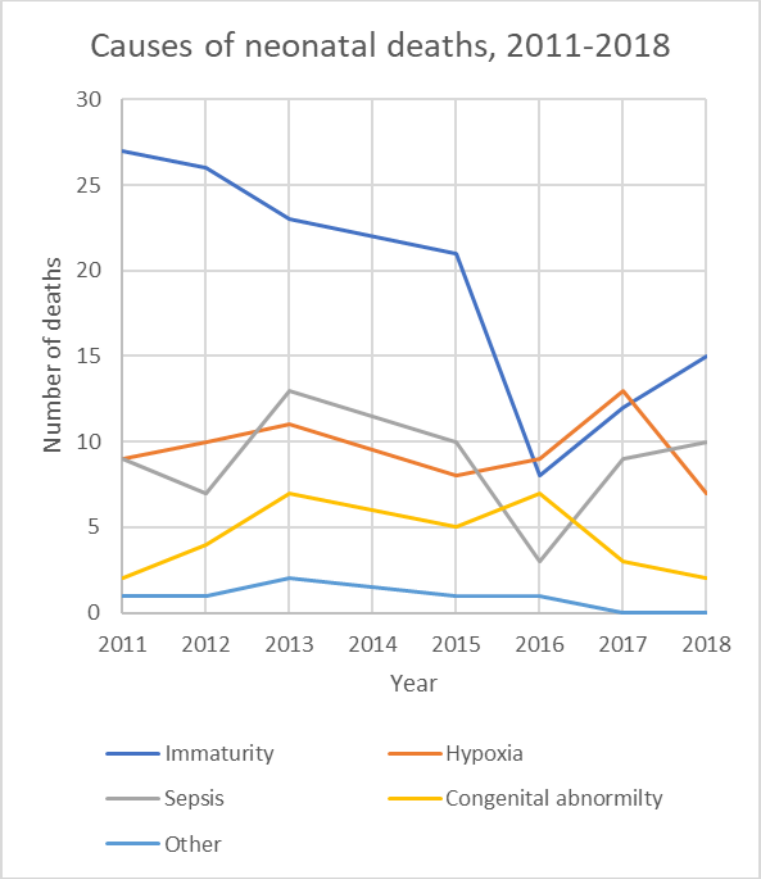
RCWMCH: Red Cross War Memorial Children's Hospital
PPIP: Perinatal Problem Identification Program
NND: Neonatal death

Table 2: Neonatal deaths per year of study

	2011 N=48	2012 N=48	2013 N=56	2015 N=45	2016 N=28	2017 N=37	2018 N=34
Rate of neonatal deaths, per 1000 admissions							
All	45.2	44.6	38.3	38.6	27.3	31.6	28.2
Inborn	44.9	47.1	34.6	41.2	30.6	29.2	22.5
Outborn	49.1	36.4	50.6	31.6	18.3	38.2	52.4
Causes of death by PPIP Category							
Immaturity	27 (56%)	26 (54%)	23 (41%)	21 (47%)	8 (29%)	12 (32%)	15 (44%)
Hypoxia	9 (19%)	10 (21%)	11 (20%)	8 (18%)	9(32%)	13 (35%)	7 (21%)
Sepsis	9 (19%)	7 (15%)	13 (23%)	10 (22%)	3 (11%)	9 (24%)	10 (29%)
Congenital abnormality	2 (4%)	4 (8%)	7 (13%)	5 (11%)	7 (25%)	3 (8%)	2 (6%)
Other	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (4%)	0	0
Birth weight categories of neonatal deaths							
Inborn:							
<1000g	25 (52%)	18 (38%)	12 (21%)	19 (42%)	5 (18%)	6 (16%)	12 (35%)
1000-1499g	2 (4%)	5 (10%)	8 (14%)	5 (11%)	1 (4%)	7 (19%)	3 (9%)
1500-2499g	4 (8%)	6 (13%)	6 (11%)	2 (4%)	7 (25%)	7 (19%)	4 (12%)
≥2500	5 (10%)	10 (21%)	13 (23%)	9 (20%)	10 (36%)	5 (14%)	3 (9%)
Outborn:							
<1000g	5 (10%)	5 (10%)	9 (16%)	2 (4%)	2 (7%)	3 (8%)	7 (21%)
1000-1499g	2 (4%)	1 (2%)	4 (7%)	1 (2%)	1 (4%)	3 (8%)	2 (6%)
1500-2499g	2 (4%)	3 (6%)	0	3 (7%)	0	4 (11%)	1 (3%)
≥2500	3 (6%)	0	4 (7%)	4 (9%)	2 (7%)	2 (5%)	2 (6%)
Age at death, days: median (IQR)	2 (1 – 4)	2 (1 – 4)	2.5 (1 -5)	1 (0 – 2)	1 (0 – 4)	1 (1 – 5)	1 (1 – 9)
Neonatal death category							
Early NND	41 (85%)	44 (92%)	46 (82%)	40 (89%)	25 (86%)	31 (84%)	24 (71%)
Late NND	7 (15%)	4 (8%)	10 (18%)	5 (11%)	4 (14%)	6 (16%)	10 (29%)
Specific causes of death							
HIE	3 (6%)	6 (13%)	6 (11%)	5 (11%)	6 (21%)	3 (8%)	3 (9%)
MAS/PPHN	5 (10%)	3 (6%)	4 (7%)	2 (4%)	3 (11%)	5 (13%)	3 (9%)
NEC	4 (8%)	3 (6%)	5 (9%)	4 (8%)	0	3 (8%)	0
Congenital syphilis	1 (2%)	1 (2%)	2 (4%)	0	0	0	0
Other sepsis	4 (8%)	3 (6%)	6 (11%)	6 (13%)	3 (11%)	6 (16%)	10 (29%)
HIV exposed	7 (15%)	9 (19%)	15 (27%)	14 (31%)	4 (14%)	15 (41%)	12 (35%)

PPIP: Perinatal Problem Identification Program
NND: Neonatal death
HIE: Hypoxic ischaemic encephalopathy
MAS: Meconium aspiration syndrome
PPHN: Persistent pulmonary hypertension of the newborn
NEC: Necrotising enterocolitis

Figure 1: Causes of neonatal deaths, 2011-2018



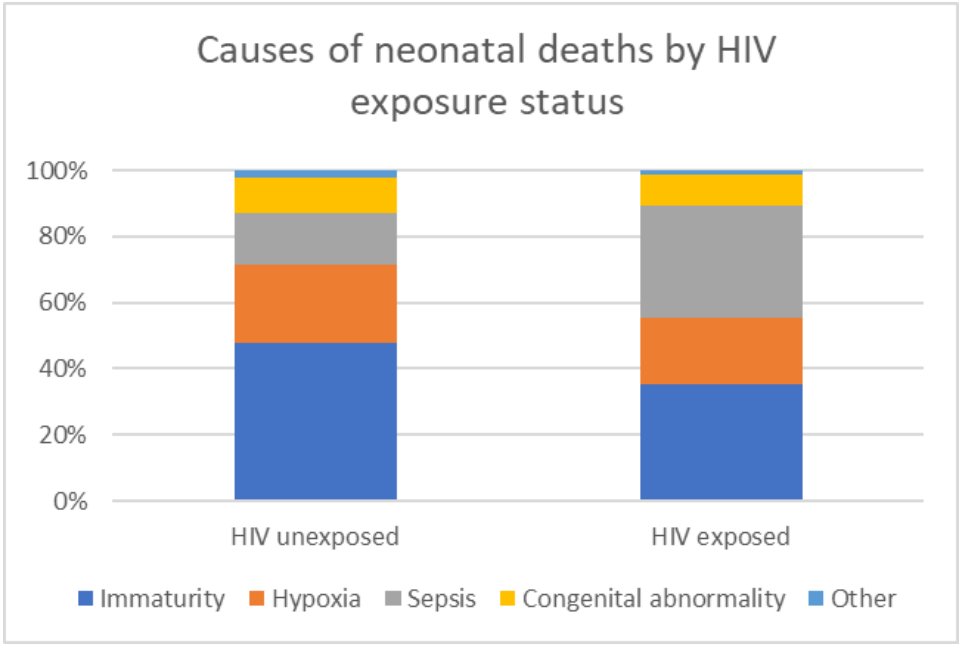
Supplementary table 1: Mean neonatal deaths per month, compared to recorded neonatal deaths in 2014, to illustrate incomplete data for several months

Month	Mean number of deaths per month, 2011-2013 and 2015-2018	Neonatal death, per month, in 2014
January	4.3	2
February	2.7	1
March	4.4	3
April	3.3	0
May	5.9	3
June	2.4	2
July	3.9	0
August	2.6	3
September	2.9	1
October	3.3	2
November	2.3	0
December	4.1	4

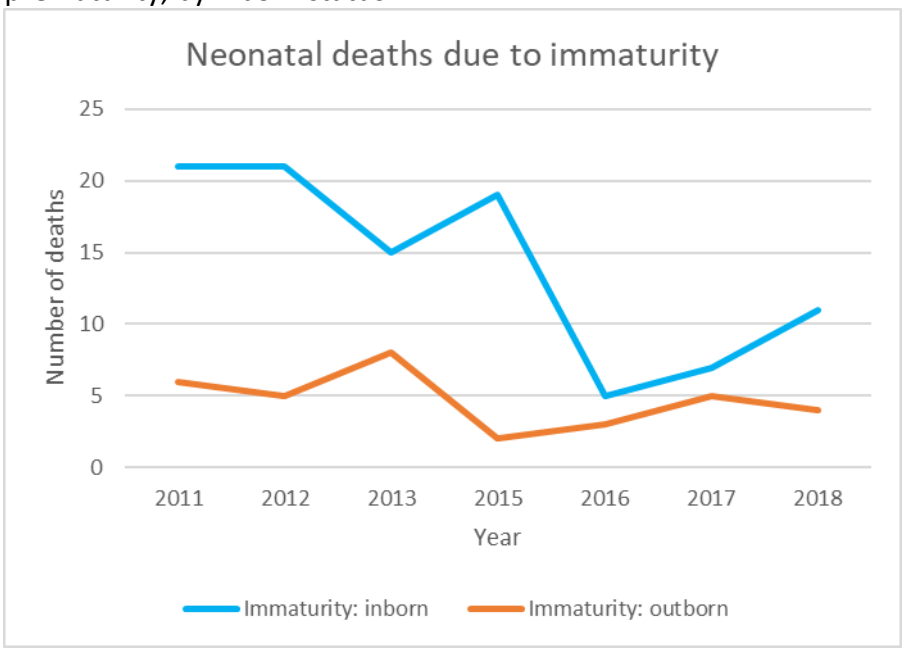
Supplementary Table 2: Cause of death of inborn and outborn neonates, by time of death

Early neonatal deaths	Outborn, n(%) n=60	Inborn, n(%) n=190	Total, n(%) n=250
Immaturity	31 (52%)	94 (49%)	125 (50%)
Hypoxia	13 (22%)	51 (27%)	64 (26%)
Infection	14 (23%)	20 (11%)	34 (14%)
Congenital anomaly	1 (2%)	22 (12%)	23 (9%)
Other	1 (2%)	3 (2%)	4 (2%)
Late neonatal deaths	Outborn, n(%) n=17	Inborn, n(%) n=29	Total, n(%) n=46
Immaturity	2 (12%)	5 (17%)	7 (15%)
Hypoxia	0	3 (10%)	3 (7%)
Infection	11 (65%)	16 (55%)	27 (59%)
Congenital anomaly	2 (12%)	5 (17%)	7 (15%)
Other	2 (12%)	0	2 (4%)

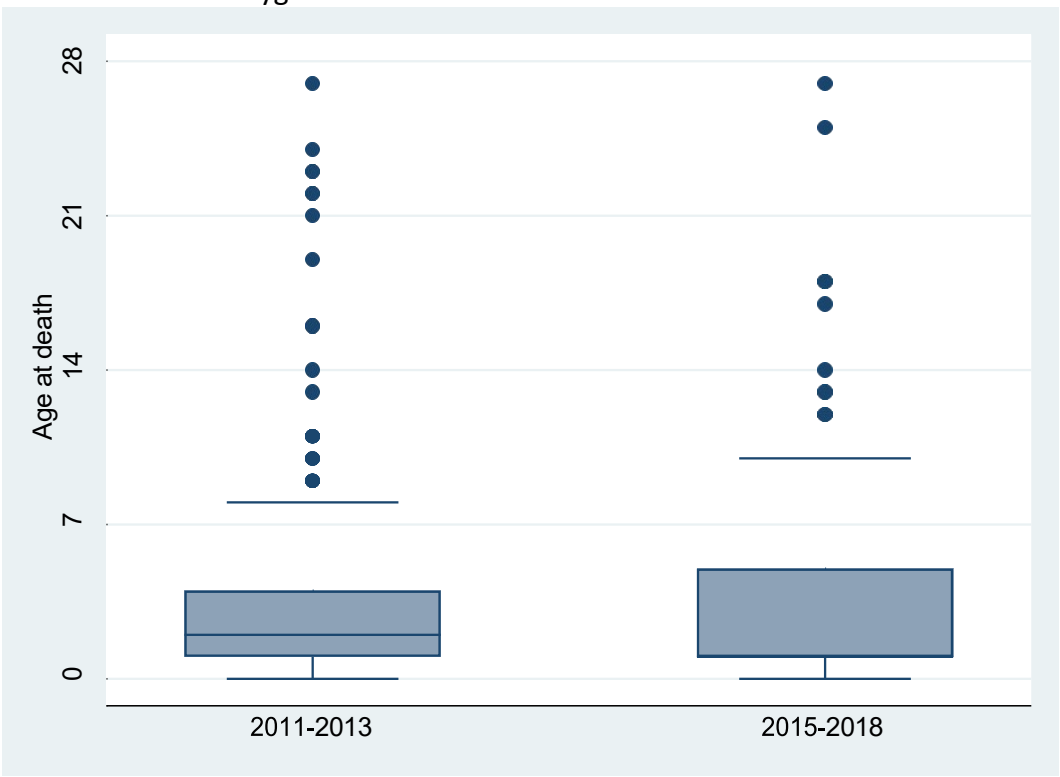
Supplementary figure 1: Causes of death of HIV-exposed and HIV unexposed neonates



Supplementary fig 2: Decreases in numbers of neonatal deaths due to prematurity, by inborn status



Supplementary fig 3: Age at death, before and after implementation of high flow nasal cannula oxygen



Appendix 1:

HREC approval

Appendix 2:

Instructions for authors

Appendix 3:

Accepted manuscript (pre-publication pdf)

South African Journal of Child Health

In-hospital neonatal mortality in a level-two hospital in Cape Town, South Africa

--Manuscript Draft--

Manuscript Number:	SAJCH01964R1
Article Type:	Original Research
Keywords:	Neonatal mortality; early neonatal death; neonatal intensive care; respiratory distress syndrome
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Manuscript Region of Origin:	SOUTH AFRICA
Abstract:	Abstract Background Neonatal mortality (deaths in the first 28 days of life) is a major contributor to under-5 mortality in South Africa. Many advances in neonatal care have been introduced, but the impact of these interventions has not been studied outside of tertiary academic centers. Objectives To describe neonatal mortality in the neonatal high care unit at New Somerset Hospital in Cape Town, South Africa, over an 8 year period. Methods Neonatal deaths were captured and entered into a database; deaths were coded according to Perinatal Problem Identification Program categories. Results Neonatal deaths from 2011 to 2018 were analyzed, excluding 2014. There were 296 neonatal deaths; median birthweight of neonatal deaths was 1140g (interquartile range (IQR) 790 – 2420g); median gestation was 29 weeks (IQR 25 – 38). Immaturity (132/296, 45%) was the most common cause of death, followed by hypoxia (67/296, 23%) and infections (61/296, 21%). There were 250 (84%) neonatal deaths in the first week of life; there was a trend towards decreasing number of neonatal deaths (from 48 in 2011 to 34 in 2018), and rate of deaths (from 45.2 per 1000 admissions to 28.2 per 1000 admissions). This was driven by decreased deaths due to immaturity; number of deaths due to other causes remained approximately constant. Conclusions We observed decreasing number of neonatal deaths and rate of deaths per 1000 admissions, with the largest decrease due to prematurity. Advances in respiratory care for preterm neonates may have contributed to decreased mortality due to immaturity. Upstream obstetric interventions will be required to address hypoxia-related causes of neonatal mortality.

In-hospital neonatal mortality in a level-two hospital in Cape Town, South Africa

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Introduction

Neonatal mortality (deaths in the first 28 days of life) has been a major contributor to under-5 mortality in South Africa, accounting for a third of under-5 deaths in 2015.[1] Due to improvements in management of HIV, pneumonia and gastroenteritis,[2] under-5 child mortality in South Africa decreased dramatically over the last 20 years, from a peak of 80 deaths per 1000 live births at the height of the HIV epidemic in 2004[3] to 34 deaths per 1000 live births in 2018.[2] However, neonatal mortality in South Africa has remained static at 11-12 deaths per 1000 live births for nearly 20 years,[2 3] so the relative contribution of neonatal mortality to total under-5 mortality has increased from 14% in 2002 to 32% in 2018.[2] Neonatal mortality must be addressed if South Africa is to meet target 3.2.12 of the Sustainable Development Goals (SDG's) by 2030, namely under-5 child mortality of less than 25 deaths per 1000 live births.[1] ~~? by 2030~~

The leading causes of under-5 mortality in South Africa are prematurity, asphyxia, HIV/AIDS, pneumonia and diarrhoeal diseases;[1 3] neonatal sepsis is also a major contributor to both early (day 1-7) and late (day 8-28) neonatal deaths.[4] Much research into the cause of neonatal deaths in South Africa and potential modifiable factors has been performed. Most pooled neonatal death surveys focus on causes of early neonatal deaths, and late NND's are under-reported.[5 -6] In a retrospective database review of 142 hospitals between October 1999 and September 2003, Velaphi et al described 4502 neonatal deaths. Prematurity accounted for 35% of deaths and 32% of deaths were due to asphyxia-

hypoxia.[7] Early continuous positive airway pressure (CPAP)[8] and exogenous surfactant therapy[9] has improved survival of extremely low birth weight neonates (ELBW) in tertiary neonatal units. High flow nasal cannula oxygen (HFNC) has been used for pre-term neonates instead of CPAP with good results.[10] Furthermore, there is evidence that outborn neonates transferred to tertiary neonatal centers have worse outcomes than inborn neonatbabies.[11] ~~or shoul there be a definition of outborn v inborn as an introductory sentence followed by the statement " furthermore"?~~ However ,there is little evidence regarding ~~outcomes of introduction of CPAP and HFNC~~impacts of these recent improvements in neonatal care -on neonatal mortality outside of tertiary academic centers; ~~,~~ nor of outcomes of outborn neonates who are transferred to non-tertiary neonatal units, where most neonatal care in South Africa is delivered.

For these reasons, we aimed to investigate neonatal mortality in a level 2 neonatal unit in Cape Town, South Africa, ~~over the period when HFNC was introduced,~~ to better understand causes of early and late neonatal mortality; and to analyze inborn vs outborn neonatal mortality. ~~; and to observe mortality changes over the period when HFNC was introduced.~~

Methods

New Somerset Hospital (NSH) is a level 2 hospital in Cape Town, South Africa. NSH performs about 6000 deliveries per year, and receives referrals from a wide geographic area, including local urban primary level delivery facilities, and remote rural hospitals up to 200km away. CPAP, surfactant and short-term ventilation (<3 days) are offered; high flow nasal cannula oxygen (HFNC) was introduced in 2015, but long-term ventilation (3 days or more), high-frequency oscillatory ventilation (HFOV), inotropic support, total parenteral nutrition are not available. N~~;~~ eonates ~~babies children~~ who require escalation of neonatal care are referred to the tertiary hospital, Groote Schuur Hospital (GSH); neonates ~~children~~ requiring surgical intervention are referred to Red Cross War Memorial Children's Hospital (RCWMCH). Neonates born at other facilities and transferred to NSH were considered "outborn".

A database of all neonatal deaths was maintained by the lead consultant in the neonatal unit. Approval to maintain the database was obtained from University of Cape Town (UCT). Human Research Ethics Committee (HREC Ref 391/2011). The neonatal mortality database included all neonates who died either on-site at New Somerset Hospital, or after

transfer to a level 3 facility (GSH or RCWMCH); information about neonatal deaths was captured in real time by doctors (registrars and medical officers) into a file kept in the neonatal high care unit (HCU) ~~should this explanation be mentioned earlier when the word was used?~~, and entered into a password-protected ~~computerized~~ database (initially an Excel spreadsheet, then an Access database) by the neonatal consultant on a weekly basis. Variables included gestational age, weight, sex, mode of delivery, and HIV exposure status. Early neonatal deaths were submitted to the local coordinators of the Perinatal Problem Identification Program (PPIP), ~~:~~ a structured national project for district-level longitudinal tracking of still births and early neonatal deaths. [4] Deaths were coded according to categories used by the PPIP ~~Perinatal Problem Identification Program (PPIP)[4]~~ for main causes of death (immaturity, hypoxia, sepsis, congenital anomalies and other). Birth weight was considered in the following categories: ~~classified as~~ >=2500g, ~~low birth weight (LBW,~~ 1500~~g~~-2499g~~,), very low birth weight (VLBW,~~ 1000-1499g~~) and extremely low birth weight (ELBW,~~ and <1000g~~)~~. Survival status of neonates after transfer to level 3 was determined and entered monthly. ~~The password-protected database was only accessible to the neonatal consultant.~~ An anonymous de-identified subset of data without any personal identifiers was analyzed by the investigators. This analysis was restricted to deaths occurring in the first 28 days of life. Neonatal deaths that occurred in labour ward were excluded, as they were never admitted to the neonatal unit. The study was approved by UCT Human Research Ethics Committee (HREC REF 71/2019). Permission to conduct the study was granted by the chief executive officer of NSH.

Statistical analysis

Categorical variables were compared percentages and proportions, and by chi-squared test; means were compared by t-test. C~~c~~ontinuous variables were presented as median and interquartile range (IQR) as they were not normally distributed, and compared with Mann-Whitney U test. Frequency tables, histograms and basic analyses were generated in Microsoft Excel; medians and IQR were calculated in Stata version 16.

Results

Neonatal deaths from 2011 to 2018 were compiled, with the exclusion of 2014, due to incomplete data capturing for several months of that year, supplementary table 1. In the seven~~7~~ years under review, there were 46 441 births at NSH, and 8166 admissions to the neonatal unit: 6205 (76%) of the neonatal admissions were inborn and 1961 (24%) were

transferred in from other birth units. There were 296 neonatal deaths associated with NSH HCU; 219 (74%) were inborn and 77 (26%) were outborn, either born before arrival or transferred in from a level one~~1~~ facility or maternal obstetric units~~s~~, table 1. Most of the neonatal deaths~~es~~ (221, 75%) occurred died at NSH, but 75 (25%) occurred after transfer to another unit. There were 171 (58%) males. Median birthweight was 1140g (IQR 790 – 2420); nearly half the neonatal deaths (130, 44%) ~~were~~ ELBW, had ~~2a~~ birth weight <1000g. Median gestation of neonates ~~or babies~~ who died was 29 weeks (IQR 25 – 38), with no significant difference between inborn and outborn (p=0.86). Overall, a majority of neonates (181/296, 61%) who died were delivered by normal vertex delivery (NVD) and were not HIV exposed (220/296, 74%). Median age at death was day 1 (IQR 1-4) for outborn vs day 2 (IQR 1-4) for inborn, p=0.20.

Commented [DIR1]: define

"Immaturity" was the most commonly coded cause of death (132/296, 45%); this category included neonates who had been recorded as having extreme prematurity (94, 32%), hyaline membrane disease (31, 11%) and pre-term intraventricular haemorrhage (7, 2%). "Perinatal hypoxia" included hypoxic ischaemic encephalopathy (32, 11%) and meconium aspiration syndrome (MAS) with or without~~out~~ persistent pulmonary hypertension of the newborn (PPHN) (25, 8%). Perinatal hypoxia was a more common cause of death among inborn neonates (54/219, 25%) compared to outborn neonates (13/77, 17%), but this difference was not statistically significant, p=0.16. Infection-related causes included 19 cases (6%) of necrotizing enterocolitis (NEC), 2 of which had an organism identified (one~~1~~ each of *Serratia marcescens* and *Escherischia coli*) and 17 were culture-negative. There were 38 neonatal deaths due to non-abdominal sepsis; 31/38 (82%) were culture-negative; those with positive cultures included 3 cases of *Pseudomonas aeruginosa*, and one~~1~~ case of each of *Streptococcus agalactiae*, *Candida albicans*, *Enterobacter cloacae*, and a mixed infection of *Klebsiella pneumoniae* and *Acinetobacter baumanii*. There were four~~4~~ (1%) neonatal deaths due to congenital syphilis. Infection-related causes of death were more common among outborn neonates (25/77, 32%) vs inborn neonates (36/219, 16%, p=0.003). Of the 30 neonates dying with congenital abnormalities, there were four~~4~~ with trisomy 18; 12 had multiple anomalies but not a recognizable syndrome; seven~~7~~ had congenital cardiac lesions, two~~2~~ of whom also had trisomy 21; five~~5~~ had pulmonary hypoplasia, and one~~1~~ each with a central nervous system lesion and congenital anaemia. The category of "other" causes of death included four~~4~~ neonates who had haemorrhages (one~~1~~ subaponeurotic, one~~1~~

intracerebral, two~~2~~ other exsanguinating haemorrhages) and two~~2~~ due to metabolic disorders.

Among neonates of different of birth weight categories, there were differences in method of delivery and cause of death: most ELBW neonatal deaths (107/130, 82%) followed NVD, and immaturity was the main cause of death (104/130, 80%); whereas neonatal deaths with birth weight >2500, hypoxia was the main cause (50/72, 69%) and Caesarean section was the most common delivery method (39/72, 54%), table 1. There were no significant differences in age at death among neonates of different birth weight categories.

Throughout the study period, antenatal HIV prevalence among pregnant women remained constant at about 20%; there were similar numbers of deaths of HIV-exposed neonates in all weight categories, table 1. There was a higher proportion of HIV exposed neonates dying ~~to~~ due to infectious causes (26/61, 43%) compared to other causes (50/235, 21%, p=0.001), Supplementary fig 1.

There was a gradual trend towards decreasing number of neonatal deaths (from 48 in 2011 to 34 in 2018) and rate of deaths (from 45.2 per 1000 admissions to 28.2 per 1000 admissions, table 2). This was largely driven by decreased deaths due to immaturity, from 27 (56%) in 2011 to 15 (44%) in 2018, figure 1; deaths among~~in~~ ELBW decreased from 25 (52%) to 12 (35%), table 2. Number of deaths in other birth weight categories and due to other causal categories remained approximately constant, table 2. Mean number of deaths due to immaturity before 2014 (average 25.3 per year) was significantly less than mean number of deaths after 2014 (average 14.0 per year, p=0.01). The decrease in number of deaths due to immaturity was more marked in neonates who were in inborn (from 21 in 2011 to 11 in 2018) compared to those who were outborn (from six~~6~~ to four~~4~~), supplementary figure 2. There were four~~4~~ deaths due to congenital syphilis prior to 2015 and none after 2015. Age at death after 2015 was lower (median 1 day, IQR 1 – 5) compared to neonates born before 2015 (median 2 days, IQR 1 – 4), supplementary figure 3; but this was not statistically significant, p=0.86.

Discussion

In this retrospective observational study, we observed decreasing numbers of neonatal deaths and decreased neonatal mortality rate among both inborn and outborn neonates; the decrease

in number deaths was more marked for deaths due to immaturity than for other cause of death codes. Over the same period of time, neonatal death rate in South Africa remained almost unchanged (between 11 and 12 deaths per 1000 live births~~,~~[2]); in Cape Town (Metro West), early neonatal deaths decreased from 7.6 to 6.4 deaths per 1000 live births.(New Somerset Hospital 2018 PPIP report, Dr Lizel Jacobs, personal communication)

Possible reasons for the observed decrease in neonatal deaths due to immaturity and in neonates in the lowest birth weight category through the course of the study period may be due to changes in policy regarding respiratory support for preterm neonates. Prior to 2015, neonates needing respiratory support received low-flow, non-humidified, blended oxygen. Limited CPAP machines were available for neonates weighing >1000g and if gestation was at least 28 weeks. From 2015, warmed humified blended high flow nasal cannula oxygen was available for all neonates, irrespective of weight or gestational age. From 2017, CPAP and surfactant were made available to neonates with birth weight >800g if gestational age was at least 28 weeks. High flow nasal cannula (HFNC) oxygen therapy in preterm infants has been associated with similar outcomes to nasal continuous airway pressure (CPAP) with fewer complications and less nasal trauma.[12] It is possible that the introduction of early HFNC in 2015 was associated with improved survival of preterm inborn neonates. The reason that deaths of outborn preterm neonates did not decrease to the same extent as inborn preterm neonates may be due to delays in transport from other facilities; neonates may have spent many hours receiving unheated non-humidified oxygen before admission to NSH, which may have caused hypothermia, atelectasis and lung inflammation.[11] Outborn neonates were also more likely to die of infectious-related causes: it is possible that potential improvements in respiratory care were mitigated by ongoing high risk of exposure to infection while in transit to NSH. It is difficult to see from this data whether decreasing the threshold to qualify for CPAP and surfactant ~~form~~in 2017 had any further impact on neonatal mortality. There had been ~~was~~ some concern that introduction of HFNC in 2014 ~~or 2015~~may prolong survival of ELBW neonates beyond day 7, but that most of these neonates would subsequently die of NEC or sepsis. However, since we did not observe an increase in late deaths from other causes, and ~~that~~ the age at death did not change throughout the study period, we believe that the observed decrease in early deaths due to immaturity is real, and is not simply due to shifting the mortality burden into a different category. There was some turnover in doctors working in the unit, but there was low turnover of nursing staff; there

were no other major changes in practice or policy regarding management of perinatal hypoxia, suspected sepsis or other neonatal conditions during~~over~~ the period under review.

The number of deaths due to hypoxia did not change much over the study period. Throughout the study period, NSH neonatal unit practiced therapeutic hypothermia for moderate / severe hypoxic ischaemic encephalopathy, and used amplitude-integrated electroencephalograms to monitor cerebral function in neonates with brain injury. However, addressing deaths due to perinatal hypoxia will require obstetric interventions and labour ward management; improved neonatal care will not be sufficient to substantially reduce hypoxia-related deaths.[13] There were ~~more~~ relatively more deaths due to hypoxia among inborn neonates compared to those referred in from other facilities. It is likely that the most severely brain injured neonates who were born at other facilities demised within a few hours of life, before the ambulance transport could bring them to NSH.

The striking decrease in hospital-related neonatal deaths has not been seen in the annual PPIP reports. There are a number of reasons for this. PPIP reports early NND's according to the delivery unit, and includes all neonates who die in labour ward or after admission to a neonatal unit. In this analysis, as we were only considering in-hospital mortality of the neonatal unit, we excluded all labour-ward deaths, but we included outborn neonates~~babies~~ who were admitted to our unit if they subsequently died~~ in our unit.~~ For this reason, PPIP stats are a more sensitive longitudinal indicator of trends for delivery units and labour wards; the current analysis is better suited to detect trends in survival that are affected by changes in neonatal practice, not labour ward management.

There was a low rate of blood culture positivity among neonates who were attributed an "infection-related" cause of death. Although the unit policy is to always draw a blood culture before starting or escalating antibiotics, it is possible that some critically ill neonates may have died before cultures could be drawn, or that inadequate blood volumes were drawn,[14] and this resulted in low culture positivity; or that true pathogen growth was masked by skin contaminants.[15] It is also possible that some of neonatal deaths labelled as "infection-related" may have been misclassified: neonates who had a clinical deterioration and demised may actually have had underlying cardiac or metabolic disease that was not diagnosed.

There is good evidence that both HIV-infected and HIV-exposed uninfected (HEU) infants have higher rates of infectious morbidity than HIV-unexposed infants.[16 17] However the higher proportion of infection-related deaths among HIV-exposed neonates is difficult to interpret, as most neonates did not have nucleic-acid testing at the time of death. Universal antiretroviral therapy for pregnant women for prevention of mother to child transmission of HIV (PMTCT) was introduced in 2013[18] but universal birth PCR testing was only introduced in 2015;[19] it is possible that some considered to be "HIV exposed" were actually *in utero* HIV infected, and already had profound immune compromise at the time of death.

There are a number of important limitations with this data analysis. This was a retrospective review of an existing database, therefore no patient folders were reviewed or interrogated regarding possible adverse outcomes. We accepted the clinical judgement of the attending clinician at the time the data were captured regarding the likely cause and category of death. However, misclassification of causes of death is possible, as very few autopsies were performed. As mentioned above, cardiac or metabolic diseases may have been misclassified as "infection-related" deaths. Annual total numbers of births in labour ward and admissions to the neonatal unit were available; however as this was not disaggregated by birth weight categories, it is not possible to calculate a neonatal mortality rate per birth weight category as the denominator for each birth weight category is not known. It would have been valuable to ~~be able to~~ calculate early and late neonatal death rates by weight category, to observe if any changes occurred during the period under review. Data collection in 2014 was obviously incomplete: for 11 months of that year the number of deaths were far below the mean number of deaths for the rest of the study period, and there were three ~~there were many~~ months with no deaths recorded at all. I~~; it~~t would have been inappropriate to include that year. ~~was easier to exclude that year altogether.~~ However it is possible that some deaths were missed and not entered into the database: the same paediatrician supervised the unit from the end of 2014 till 2018, and the same data capture systems were in place; but with a manual system of data capture and data entry, it is possible that some deaths may have been missed. PPIP does not capture access to neonatal therapies (HFNC, CPAP, surfactant, therapeutic hypothermia): it was not possible to compare impact of neonatal therapies within the neonatal unit over time as this data was not available.

Conclusion

In this retrospective analysis of an existing database, we observed decreasing number of neonatal deaths over the period 2011-2018; the category with the largest decrease was inborn deaths due to prematurity, while all other numbers of deaths due to all other causes remained approximately the same. This period coincided with the introduction of high flow nasal cannula oxygen into the neonatal unit, and subsequent expansion of CPAP eligibility criteria from 1000g to 800g. These advances in respiratory support may have contributed to some of the observed decreased deaths due to prematurity. Combinations of interventions may be required to reduce the residual burden of neonatal mortality in South Africa. Expansion of access to HFNC and CPAP may reduce deaths due to prematurity, but other upstream interventions, including improved access to antenatal care (like steroids for preterm labour) and other obstetric interventions in labour ward, will be required to address the residual burden of immaturity- and hypoxia-related causes of neonatal mortality.

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Neonatal mortality_tables and figures

Table 1: Characteristics of neonatal deaths by birth weight category

	Birthweight <1000g N=130	Birthweight 1000-1499g N=45	Birthweight 1500-2499g N=49	Birthweight ≥2500 N=72	Total N=296
Place born:					
Inborn	97 (75%)	31 (69%)	36 (73%)	55 (76%)	219 (74%)
BBA	14 (11%)	7 (16%)	3 (6%)	4 (6%)	28 (9%)
Vanguard MOU	6 (5%)	2 (4%)	5 (10%)	4 (6%)	17 (6%)
Vredenburg Hospital	6 (5%)	1 (2%)	2 (4%)	6 (7%)	14 (5%)
Wesfleur Hospital	4 (3%)	2 (4%)	0	2 (3%)	8 (3%)
Other	3 (2%)	2 (4%)	3 (6%)	2 (3%)	10 (3%)
Place died					
NSH	127 (98%)	25 (55%)	28 (57%)	41 (57%)	221 (75%)
RCWMCH	0	3 (7%)	6 (12%)	2 (3%)	11 (4%)
GSH	3 (2%)	16 (36%)	14 (29%)	29 (40%)	62 (21%)
Other	0	1 (2%)	1 (2%)	0	1 (0.7%)
Male sex	78 (60%)	25 (56%)	28 (57%)	40 (56%)	171 (58%)
HIV exposure status					
Unexposed	97 (75%)	31 (69%)	36 (73%)	36 (73%)	220 (74%)
Exposed	33 (25%)	14 (31%)	13 (27%)	16 (22%)	76 (26%)
Delivery method					
Normal vertex delivery	107 (82%)	20 (44%)	26 (53%)	28 (39%)	181 (61%)
Caesarean section	11 (8%)	23 (51%)	21 (43%)	39 (54%)	94 (32%)
Vaginal breech	12 (9%)	2 (4%)	1 (2%)	1 (1%)	16 (5%)
Forceps	0	0	0	4 (6%)	4 (1%)
Vacuum	0	0	1 (2%)	0	1 (0.3%)
Cause of death by PPIP category					
Immaturity	104 (80%)	24 (53)	4 (8%)	0	132 (45%)
Hypoxia	0	4 (9%)	13 (27%)	50 (69%)	67 (23%)
Infection	25 (19%)	15 (33%)	14 (29%)	7 (10%)	61 (21%)
Congenital anomaly	1 (1%)	2 (4%)	17 (35%)	10 (14%)	30 (10%)
Other	0	0	1 (2%)	5 (7%)	6 (2%)
Age at death, days: median (IQR)	1 (0 – 4)	2 (1 – 6)	2 (1 – 5)	2 (1 – 3)	1 (1 – 4)
Neonatal death category					
Early NND	108 (83%)	35 (78%)	41 (84%)	66 (92%)	250 (84%)
Late NND	22 (17%)	10 (22%)	8 (16%)	6 (8%)	46 (17%)

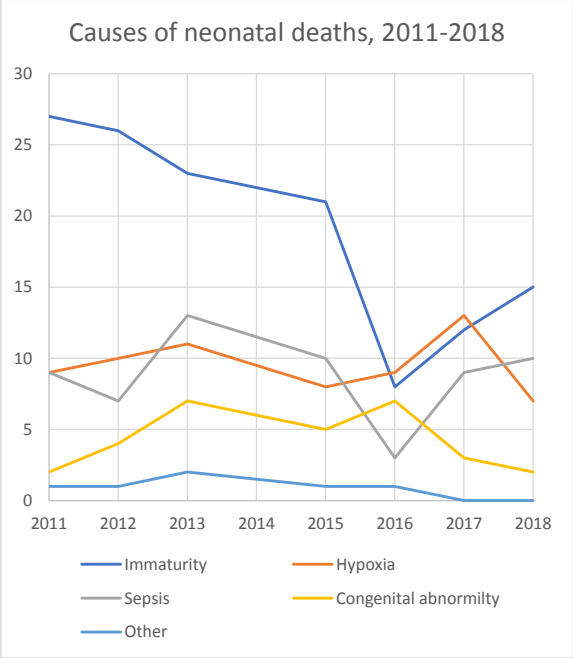
BBA: Born before arrival
MOU: Midwife obstetric unit
NSH: Nnew Somerset Hospital
GSH: Groote Schuur Hospital
RCWMCH: Red Cross War Memorial Children's Hospital
PPIP: Perinatal Problem Identification Program
NND: Neonatal death

Table 2: Neonatal deaths per year of study

	2011 N=48	2012 N=48	2013 N=56	2015 N=45	2016 N=28	2017 N=37	2018 N=34
Rate of neonatal deaths, per 1000 admissions							
All	45.2	44.6	38.3	38.6	27.3	31.6	28.2
Inborn	44.9	47.1	34.6	41.2	30.6	29.2	22.5
Outborn	49.1	36.4	50.6	31.6	18.3	38.2	52.4
Causes of death by PPIP category							
Immaturity	27 (56%)	26 (54%)	23 (41%)	21 (47%)	8 (29%)	12 (32%)	15 (44%)
Hypoxia	9 (19%)	10 (21%)	11 (20%)	8 (18%)	9(32%)	13 (35%)	7 (21%)
Sepsis	9 (19%)	7 (15%)	13 (23%)	10 (22%)	3 (11%)	9 (24%)	10 (29%)
Congenital abnormality	2 (4%)	4 (8%)	7 (13%)	5 (11%)	7 (25%)	3 (8%)	2 (6%)
Sepsis	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (4%)	0	0
Birth weight categories of neonatal deaths							
Inborn:							
<1000g	25 (52%)	18 (38%)	12 (21%)	19 (42%)	5 (18%)	6 (16%)	12 (35%)
1000-1499g	2 (4%)	5 (10%)	8 (14%)	5 (11%)	1 (4%)	7 (19%)	3 (9%)
1500-2499g	4 (8%)	6 (13%)	6 (11%)	2 (4%)	7 (25%)	7 (19%)	4 (12%)
≥2500	5 (10%)	10 (21%)	13 (23%)	9 (20%)	10 (36%)	5 (14%)	3 (9%)
Outborn:							
<1000g	5 (10%)	5 (10%)	9 (16%)	2 (4%)	2 (7%)	3 (8%)	7 (21%)
1000-1499g	2 (4%)	1 (2%)	4 (7%)	1 (2%)	1 (4%)	3 (8%)	2 (6%)
1500-2499g	2 (4%)	3 (6%)	0	3 (7%)	0	4 (11%)	1 (3%)
≥2500	3 (6%)	0	4 (7%)	4 (9%)	2 (7%)	2 (5%)	2 (6%)
Age at death, days: median (IQR)	2 (1 – 4)	2 (1 – 4)	2.5 (1 -5)	1 (0 – 2)	1 (0 – 4)	1 (1 – 5)	1 (1 – 9)
Neonatal death category							
Early NND	41 (85%)	44 (92%)	46 (82%)	40 (89%)	25 (86%)	31 (84%)	24 (71%)
Late NND	7 (15%)	4 (8%)	10 (18%)	5 (11%)	4 (14%)	6 (16%)	10 (29%)
Specific causes of death							
HIE	3 (6%)	6 (13%)	6 (11%)	5 (11%)	6 (21%)	3 (8%)	3 (9%)
MAS/PPHN	5 (10%)	3 (6%)	4 (7%)	2 (4%)	3 (11%)	5 (13%)	3 (9%)
NEC	4 (8%)	3 (6%)	5 (9%)	4 (8%)	0	3 (8%)	0
Congenital syphilis	1 (2%)	1 (2%)	2 (4%)	0	0	0	0
Other sepsis	4 (8%)	3 (6%)	6 (11%)	6 (13%)	3 (11%)	6 (16%)	10 (29%)
HIV exposed	7 (15%)	9 (19%)	15 (27%)	14 (31%)	4 (14%)	15 (41%)	12 (35%)

PPIP: Perinatal Problem Identification Program
NND: Neonatal death
HIE: Hypoxic ischaemic encephalopathy
MAS: Meconium aspiration syndrome
PPHN: Persistent pulmonary hypertension of the newborn
NEC: Necrotising enterocolitis

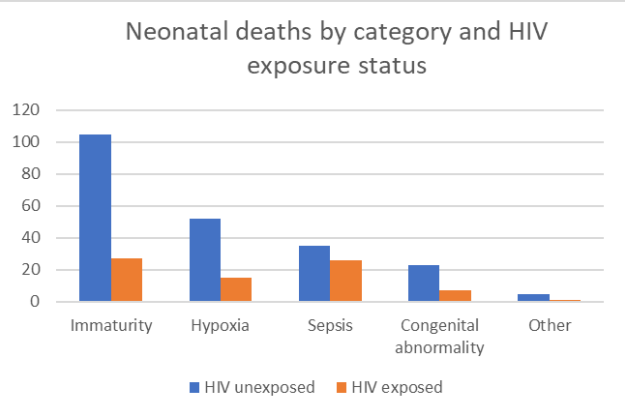
Figure 1: Causes of neonatal deaths, 2011-2018



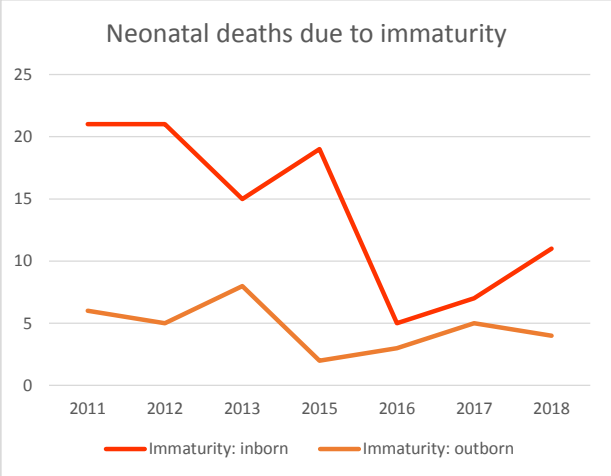
Supplementary table 1: Mean neonatal deaths per month, compared to recorded neonatal deaths in 2014, to illustrate incomplete data for several months

Month	Mean number of deaths per month, 2011-2013 and 2015-2018	Neonatal death, per month, in 2014
January	4.3	2
February	2.7	1
March	4.4	3
April	3.3	0
May	5.9	3
June	2.4	2
July	3.9	0
August	2.6	3
September	2.9	1
October	3.3	2
November	2.3	0
December	4.1	4

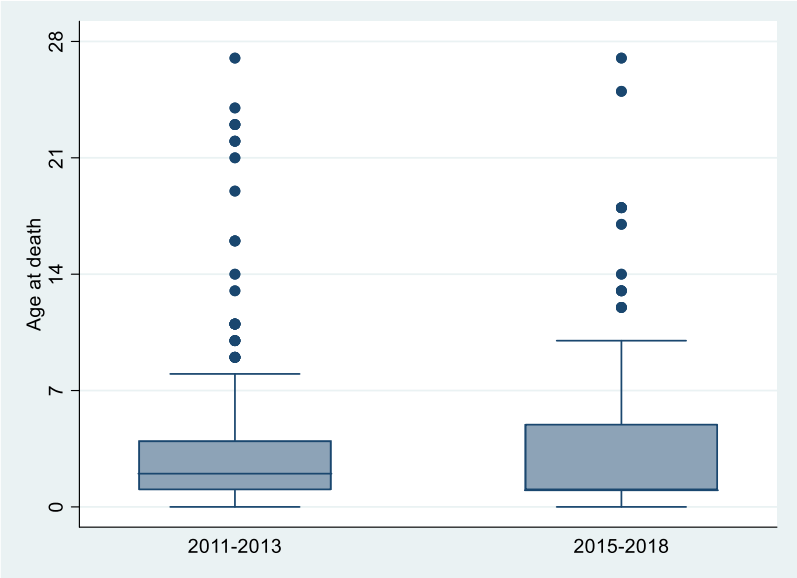
Supplementary figure 1: Causes of death of HIV-exposed and HIV unexposed neonates



Supplementary fig 2: Decreases in numbers of neonatal deaths due to prematurity, by inborn status



Supplementary fig 3: Age at death, before and after implementation of high flow nasal cannula oxygen



In-hospital neonatal mortality in a level-two hospital in Cape Town, South Africa

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Introduction

Neonatal mortality (deaths in the first 28 days of life) has been a major contributor to under-5 mortality in South Africa, accounting for a third of under-5 deaths in 2015.[1] Due to improvements in management of HIV, pneumonia and gastroenteritis,[2] under-5 child mortality in South Africa decreased dramatically over the last 20 years, from a peak of 80 deaths per 1000 live births at the height of the HIV epidemic in 2004[3] to 34 deaths per 1000 live births in 2018.[2] However, neonatal mortality in South Africa has remained static at 11-12 deaths per 1000 live births for nearly 20 years,[2 3] so the relative contribution of neonatal mortality to total under-5 mortality has increased from 14% in 2002 to 32% in 2018.[2] Neonatal mortality must be addressed if South Africa is to meet target 3.2.1 of the Sustainable Development Goals (SDG's) by 2030, namely under-5 child mortality of less than 25 deaths per 1000 live births.[1]

The leading causes of under-5 mortality in South Africa are prematurity, asphyxia, HIV/AIDS, pneumonia and diarrhoeal diseases;[1 3] neonatal sepsis is also a major contributor to both early (day 1-7) and late (day 8-28) neonatal deaths.[4] Much research into the cause of neonatal deaths in South Africa and potential modifiable factors has been performed. Most pooled neonatal death surveys focus on causes of early neonatal deaths, and late NND's are under-reported.[5 -6] In a retrospective database review of 142 hospitals between October 1999 and September 2003, Velaphi et al described 4502 neonatal

deaths. Prematurity accounted for 35% of deaths and 32% of deaths were due to asphyxia-hypoxia.[7] Early continuous positive airway pressure (CPAP)[8] and exogenous surfactant therapy[9] has improved survival of extremely low birth weight neonates (ELBW) in tertiary neonatal units. High flow nasal cannula oxygen (HFNC) has been used for pre-term neonates instead of CPAP with good results.[10] Furthermore, there is evidence that outborn neonates transferred to tertiary neonatal centers have worse outcomes than inborn neonates.[11] However there is little evidence regarding impacts of these recent improvements in neonatal care on neonatal mortality outside of tertiary academic centers; nor of outcomes of outborn neonates who are transferred to non-tertiary neonatal units, where most neonatal care in South Africa is delivered.

For these reasons, we aimed to investigate neonatal mortality in a level 2 neonatal unit in Cape Town, South Africa, to better understand causes of early and late neonatal mortality; and to analyze inborn vs outborn neonatal mortality.

Methods

New Somerset Hospital (NSH) is a level 2 hospital in Cape Town, South Africa. NSH performs about 6000 deliveries per year, and receives referrals from a wide geographic area, including local urban primary level delivery facilities, and remote rural hospitals up to 200km away. CPAP, surfactant and short-term ventilation (<3 days) are offered; high flow nasal cannula oxygen (HFNC) was introduced in 2015, but long-term ventilation (3 days or more), high-frequency oscillatory ventilation (HFOV), inotropic support, total parenteral nutrition are not available. Neonates who require escalation of neonatal care are referred to the tertiary hospital, Groote Schuur Hospital (GSH); neonates requiring surgical intervention are referred to Red Cross War Memorial Children's Hospital (RCWMCH). Neonates born at other facilities and transferred to NSH were considered "outborn".

A database of all neonatal deaths was maintained by the lead consultant in the neonatal unit. Approval to maintain the database was obtained from University of Cape Town (UCT). Human Research Ethics Committee (HREC Ref 391/2011). The neonatal mortality database included all neonates who died either on-site at New Somerset Hospital, or after transfer to a level 3 facility (GSH or RCWMCH); information about neonatal deaths was captured in real time by doctors (registrars and medical officers) into a file kept in the neonatal high care unit (HCU), and entered into a password-protected database (initially an

Excel spreadsheet, then an Access database) by the neonatal consultant on a weekly basis. Variables included gestational age, weight, sex, mode of delivery, and HIV exposure status. Early neonatal deaths were submitted to the local coordinators of the Perinatal Problem Identification Program (PPIP), a structured national project for district-level longitudinal tracking of still births and early neonatal deaths. [4] Deaths were coded according to categories used by the PPIP for main causes of death (immaturity, hypoxia, sepsis, congenital anomalies and other). Birth weight was considered in the following categories: >=2500g, 1500-2499g, 1000-1499g and <1000g. Survival status of neonates after transfer to level 3 was determined and entered monthly. An anonymous de-identified subset of data without any personal identifiers was analyzed by the investigators. This analysis was restricted to deaths occurring in the first 28 days of life. Neonatal deaths that occurred in labour ward were excluded, as they were never admitted to the neonatal unit. The study was approved by UCT Human Research Ethics Committee (HREC REF 71/2019). Permission to conduct the study was granted by the chief executive officer of NSH.

Statistical analysis

Categorical variables were compared percentages and proportions, and by chi-squared test; means were compared by t-test. Continuous variables were presented as median and interquartile range (IQR) as they were not normally distributed, and compared with Mann-Whitney U test. Frequency tables, histograms and basic analyses were generated in Microsoft Excel; medians and IQR were calculated in Stata version 16.

Results

Neonatal deaths from 2011 to 2018 were compiled, with the exclusion of 2014, due to incomplete data capturing for several months of that year, supplementary table 1. In the seven years under review, there were 46 441 births at NSH, and 8166 admissions to the neonatal unit: 6205 (76%) of the neonatal admissions were inborn and 1961 (24%) were transferred in from other birth units. There were 296 neonatal deaths associated with NSH HCU; 219 (74%) were inborn and 77 (26%) were outborn, either born before arrival or transferred in from a level one facility or maternal obstetric unit, table 1. Most of the neonatal deaths (221, 75%) occurred died at NSH, but 75 (25%) occurred after transfer to another unit. There were 171 (58%) males. Median birthweight was 1140g (IQR 790 – 2420); nearly half the neonatal deaths (130, 44%) had birth weight <1000g. Median gestation of neonates who died was 29 weeks (IQR 25 – 38), with no significant difference

between inborn and outborn (p=0.86). Overall, a majority of neonates (181/296, 61%) who died were delivered by normal vertex delivery (NVD) and were not HIV exposed (220/296, 74%). Median age at death was day 1 (IQR 1-4) for outborn vs day 2 (IQR 1-4) for inborn, p=0.20.

"Immaturity" was the most commonly coded cause of death (132/296, 45%); this category included neonates who had been recorded as having extreme prematurity (94, 32%), hyaline membrane disease (31, 11%) and pre-term intraventricular haemorrhage (7, 2%). "Perinatal hypoxia" included hypoxic ischaemic encephalopathy (32, 11%) and meconium aspiration syndrome (MAS) with or without persistent pulmonary hypertension of the newborn (PPHN) (25, 8%). Perinatal hypoxia was a more common cause of death among inborn neonates (54/219, 25%) compared to outborn neonates (13/77, 17%), but this difference was not statistically significant, p=0.16. Infection-related causes included 19 cases (6%) of necrotizing enterocolitis (NEC), 2 of which had an organism identified (one each of *Serratia marcescens* and *Escherischia coli*) and 17 were culture-negative. There were 38 neonatal deaths due to non-abdominal sepsis; 31/38 (82%) were culture-negative; those with positive cultures included 3 cases of *Pseudomonas aeruginosa*, and one case of each of *Streptococcus agalactiae*, *Candida albicans*, *Enterobacter cloacae*, and a mixed infection of *Klebsiella pneumoniae* and *Acinetobacter baumanii*. There were four (1%) neonatal deaths due to congenital syphilis. Infection-related causes of death were more common among outborn neonates (25/77, 32%) vs inborn neonates (36/219, 16%, p=0.003). Of the 30 neonates dying with congenital abnormalities, there were four with trisomy 18; 12 had multiple anomalies but not a recognizable syndrome; seven had congenital cardiac lesions, two of whom also had trisomy 21; five had pulmonary hypoplasia, and one each with a central nervous system lesion and congenital anaemia. The category of "other" causes of death included four neonates who had haemorrhages (one subaponeurotic, one intracerebral, two other exsanguinating haemorrhages) and two due to metabolic disorders.

Among neonates of different of birth weight categories, there were differences in method of delivery and cause of death: most ELBW neonatal deaths (107/130, 82%) followed NVD, and immaturity was the main cause of death (104/130, 80%); whereas neonatal deaths with birth weight >2500, hypoxia was the main cause (50/72, 69%) and Caesarean section was the most common delivery method (39/72, 54%), table 1. There were no significant differences in age at death among neonates of different birth weight categories.

Throughout the study period, antenatal HIV prevalence among pregnant women remained constant at about 20%; there were similar numbers of deaths of HIV-exposed neonates in all weight categories, table 1. There was a higher proportion of HIV exposed neonates dying due to infectious causes (26/61, 43%) compared to other causes (50/235, 21%, p=0.001), Supplementary fig 1.

There was a gradual trend towards decreasing number of neonatal deaths (from 48 in 2011 to 34 in 2018) and rate of deaths (from 45.2 per 1000 admissions to 28.2 per 1000 admissions, table 2). This was largely driven by decreased deaths due to immaturity, from 27 (56%) in 2011 to 15 (44%) in 2018, figure 1; deaths among ELBW decreased from 25 (52%) to 12 (35%), table 2. Number of deaths in other birth weight categories and due to other causal categories remained approximately constant, table 2. Mean number of deaths due to immaturity before 2014 (average 25.3 per year) was significantly less than mean number of deaths after 2014 (average 14.0 per year, p=0.01). The decrease in number of deaths due to immaturity was more marked in neonates who were in inborn (from 21 in 2011 to 11 in 2018) compared to those who were outborn (from six to four), supplementary figure 2. There were four deaths due to congenital syphilis prior to 2015 and none after 2015. Age at death after 2015 was lower (median 1 day, IQR 1 – 5) compared to neonates born before 2015 (median 2 days, IQR 1 – 4), supplementary figure 3; but this was not statistically significant, p=0.86.

Discussion

In this retrospective observational study, we observed decreasing numbers of neonatal deaths and decreased neonatal mortality rate among both inborn and outborn neonates; the decrease in number deaths was more marked for deaths due to immaturity than for other cause of death codes. Over the same period of time, neonatal death rate in South Africa remained almost unchanged (between 11 and 12 deaths per 1000 live births[2]); in Cape Town (Metro West), early neonatal deaths decreased from 7.6 to 6.4 deaths per 1000 live births.(New Somerset Hospital 2018 PPIP report, Dr Lizel Jacobs, personal communication)

Possible reasons for the observed decrease in neonatal deaths due to immaturity and in neonates in the lowest birth weight category through the course of the study period may be due to changes in policy regarding respiratory support for preterm neonates. Prior to 2015,

neonates needing respiratory support received low-flow, non-humidified, blended oxygen. Limited CPAP machines were available for neonates weighing >1000g and if gestation was at least 28 weeks. From 2015, warmed humified blended high flow nasal cannula oxygen was available for all neonates, irrespective of weight or gestational age. From 2017, CPAP and surfactant were made available to neonates with birth weight >800g if gestational age was at least 28 weeks. High flow nasal cannula (HFNC) oxygen therapy in preterm infants has been associated with similar outcomes to nasal continuous airway pressure (CPAP) with fewer complications and less nasal trauma.[12] It is possible that the introduction of early HFNC in 2015 was associated with improved survival of preterm inborn neonates. The reason that deaths of outborn preterm neonates did not decrease to the same extent as inborn preterm neonates may be due to delays in transport from other facilities; neonates may have spent many hours receiving unheated non-humidified oxygen before admission to NSH, which may have caused hypothermia, atelectasis and lung inflammation.[11] Outborn neonates were also more likely to die of infectious-related causes: it is possible that potential improvements in respiratory care were mitigated by ongoing high risk of exposure to infection while in transit to NSH. It is difficult to see from this data whether decreasing the threshold to qualify for CPAP and surfactant in 2017 had any further impact on neonatal mortality. There had been some concern that introduction of HFNC in 2014 may prolong survival of ELBW neonates beyond day 7, but that most of these neonates would subsequently die of NEC or sepsis. However, since we did not observe an increase in late deaths from other causes, and the age at death did not change throughout the study period, we believe that the observed decrease in early deaths due to immaturity is real, and is not simply due to shifting the mortality burden into a different category. There was some turnover in doctors working in the unit, but there was low turnover of nursing staff; there were no other major changes in practice or policy regarding management of perinatal hypoxia, suspected sepsis or other neonatal conditions during the period under review.

The number of deaths due to hypoxia did not change much over the study period. Throughout the study period, NSH neonatal unit practiced therapeutic hypothermia for moderate / severe hypoxic ischaemic encephalopathy, and used amplitude-integrated electroencephalograms to monitor cerebral function in neonates with brain injury. However, addressing deaths due to perinatal hypoxia will require obstetric interventions and labour ward management; improved neonatal care will not be sufficient to substantially reduce hypoxia-related deaths.[13] There were relatively more deaths due to hypoxia among inborn

neonates compared to those referred in from other facilities. It is likely that the most severely brain injured neonates who were born at other facilities demised within a few hours of life, before the ambulance transport could bring them to NSH.

The striking decrease in hospital-related neonatal deaths has not been seen in the annual PPIP reports. There are a number of reasons for this. PPIP reports early NND's according to the delivery unit, and includes all neonates who die in labour ward or after admission to a neonatal unit. In this analysis, as we were only considering in-hospital mortality of the neonatal unit, we excluded all labour-ward deaths, but we included outborn neonates who were admitted to our unit if they subsequently died. For this reason, PPIP stats are a more sensitive longitudinal indicator of trends for delivery units and labour wards; the current analysis is better suited to detect trends in survival that are affected by changes in neonatal practice, not labour ward management.

There was a low rate of blood culture positivity among neonates who were attributed an "infection-related" cause of death. Although the unit policy is to always draw a blood culture before starting or escalating antibiotics, it is possible that some critically ill neonates may have died before cultures could be drawn, or that inadequate blood volumes were drawn,[14] and this resulted in low culture positivity; or that true pathogen growth was masked by skin contaminants.[15] It is also possible that some of neonatal deaths labelled as "infection-related" may have been misclassified: neonates who had a clinical deterioration and demised may actually have had underlying cardiac or metabolic disease that was not diagnosed.

There is good evidence that both HIV-infected and HIV-exposed uninfected (HEU) infants have higher rates of infectious morbidity than HIV-unexposed infants.[16 17] However the higher proportion of infection-related deaths among HIV-exposed neonates is difficult to interpret, as most neonates did not have nucleic-acid testing at the time of death. Universal antiretroviral therapy for pregnant women for prevention of mother to child transmission of HIV (PMTCT) was introduced in 2013[18] but universal birth PCR testing was only introduced in 2015;[19] it is possible that some considered to be "HIV exposed" were actually *in utero* HIV infected, and already had profound immune compromise at the time of death.

There are a number of important limitations with this data analysis. This was a retrospective review of an existing database, therefore no patient folders were reviewed or interrogated regarding possible adverse outcomes. We accepted the clinical judgement of the attending clinician at the time the data were captured regarding the likely cause and category of death. However, misclassification of causes of death is possible, as very few autopsies were performed. As mentioned above, cardiac or metabolic diseases may have been misclassified as "infection-related" deaths. Annual total numbers of births in labour ward and admissions to the neonatal unit were available; however as this was not disaggregated by birth weight categories, it is not possible to calculate a neonatal mortality rate per birth weight category as the denominator for each birth weight category is not known. It would have been valuable to calculate early and late neonatal death rates by weight category, to observe if any changes occurred during the period under review. Data collection in 2014 was obviously incomplete: for 11 months of that year the number of deaths were far below the mean number of deaths for the rest of the study period, and there were three months with no deaths recorded at all. It would have been inappropriate to include that year. However it is possible that some deaths were missed and not entered into the database: the same paediatrician supervised the unit from the end of 2014 till 2018, and the same data capture systems were in place; but with a manual system of data capture and data entry, it is possible that some deaths may have been missed. PPIP does not capture access to neonatal therapies (HFNC, CPAP, surfactant, therapeutic hypothermia): it was not possible to compare impact of neonatal therapies within the neonatal unit over time as this data was not available.

Conclusion

In this retrospective analysis of an existing database, we observed decreasing number of neonatal deaths over the period 2011-2018; the category with the largest decrease was inborn deaths due to prematurity, while all other numbers of deaths due to all other causes remained approximately the same. This period coincided with the introduction of high flow nasal cannula oxygen into the neonatal unit, and subsequent expansion of CPAP eligibility criteria from 1000g to 800g. These advances in respiratory support may have contributed to some of the observed decreased deaths due to prematurity. Combinations of interventions may be required to reduce the residual burden of neonatal mortality in South Africa. Expansion of access to HFNC and CPAP may reduce deaths due to prematurity, but other upstream interventions, including improved access to antenatal care (like steroids for

preterm labour) and other obstetric interventions in labour ward, will be required to address the residual burden of immaturity- and hypoxia-related causes of neonatal mortality.

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Neonatal mortality_tables and figures

Table 1: Characteristics of neonatal deaths by birth weight category

	Birthweight <1000g N=130	Birthweight 1000-1499g N=45	Birthweight 1500-2499g N=49	Birthweight ≥2500 N=72	Total N=296
Place born:					
Inborn	97 (75%)	31 (69%)	36 (73%)	55 (76%)	219 (74%)
BBA	14 (11%)	7 (16%)	3 (6%)	4 (6%)	28 (9%)
Vanguard MOU	6 (5%)	2 (4%)	5 (10%)	4 (6%)	17 (6%)
Vredenburg Hospital	6 (5%)	1 (2%)	2 (4%)	6 (7%)	14 (5%)
Wesfleur Hospital	4 (3%)	2 (4%)	0	2 (3%)	8 (3%)
Other	3 (2%)	2 (4%)	3 (6%)	2 (3%)	10 (3%)
Place died					
NSH	127 (98%)	25 (55%)	28 (57%)	41 (57%)	221 (75%)
RCWMCH	0	3 (7%)	6 (12%)	2 (3%)	11 (4%)
GSH	3 (2%)	16 (36%)	14 (29%)	29 (40%)	62 (21%)
Other	0	1 (2%)	1 (2%)	0	1 (0.7%)
Male sex	78 (60%)	25 (56%)	28 (57%)	40 (56%)	171 (58%)
HIV exposure status					
Unexposed	97 (75%)	31 (69%)	36 (73%)	36 (73%)	220 (74%)
Exposed	33 (25%)	14 (31%)	13 (27%)	16 (22%)	76 (26%)
Delivery method					
Normal vertex delivery	107 (82%)	20 (44%)	26 (53%)	28 (39%)	181 (61%)
Caesarean section	11 (8%)	23 (51%)	21 (43%)	39 (54%)	94 (32%)
Vaginal breech	12 (9%)	2 (4%)	1 (2%)	1 (1%)	16 (5%)
Forceps	0	0	0	4 (6%)	4 (1%)
Vacuum	0	0	1 (2%)	0	1 (0.3%)
Cause of death by PPIP category					
Immaturity	104 (80%)	24 (53)	4 (8%)	0	132 (45%)
Hypoxia	0	4 (9%)	13 (27%)	50 (69%)	67 (23%)
Infection	25 (19%)	15 (33%)	14 (29%)	7 (10%)	61 (21%)
Congenital anomaly	1 (1%)	2 (4%)	17 (35%)	10 (14%)	30 (10%)
Other	0	0	1 (2%)	5 (7%)	6 (2%)
Age at death, days: median (IQR)	1 (0 – 4)	2 (1 – 6)	2 (1 – 5)	2 (1 – 3)	1 (1 – 4)
Neonatal death category					
Early NND	108 (83%)	35 (78%)	41 (84%)	66 (92%)	250 (84%)
Late NND	22 (17%)	10 (22%)	8 (16%)	6 (8%)	46 (17%)

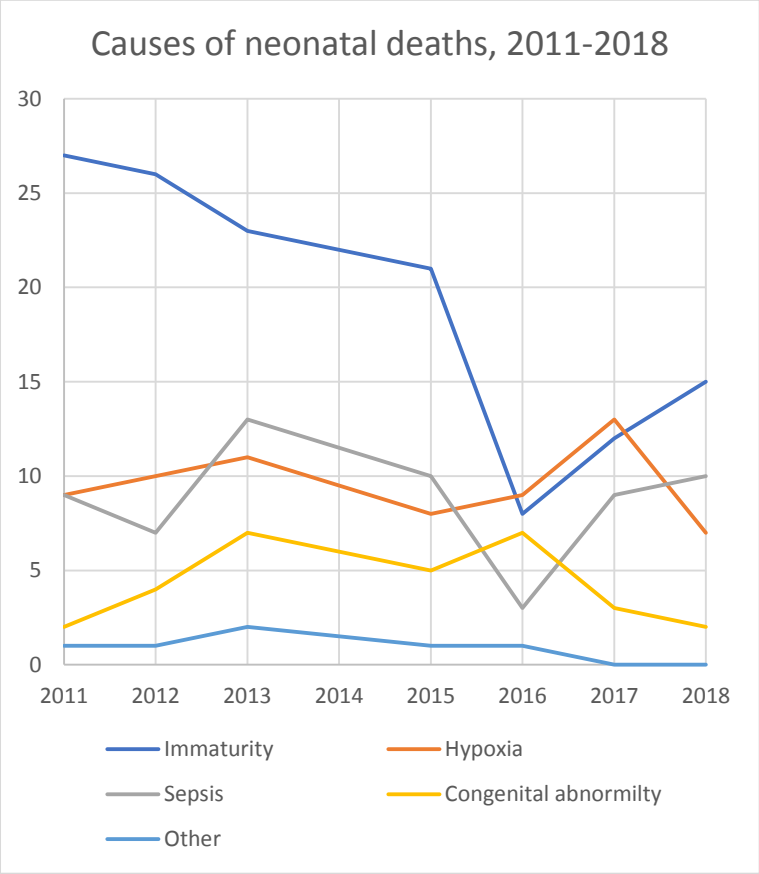
BBA: Born before arrival
MOU: Midwife obstetric unit
NSH: New Somerset Hospital
GSH: Groote Schuur Hospital
RCWMCH: Red Cross War Memorial Children's Hospital
PPIP: Perinatal Problem Identification Program
NND: Neonatal death

Table 2: Neonatal deaths per year of study

	2011 N=48	2012 N=48	2013 N=56	2015 N=45	2016 N=28	2017 N=37	2018 N=34
Rate of neonatal deaths, per 1000 admissions							
All	45.2	44.6	38.3	38.6	27.3	31.6	28.2
Inborn	44.9	47.1	34.6	41.2	30.6	29.2	22.5
Outborn	49.1	36.4	50.6	31.6	18.3	38.2	52.4
Causes of death by PPIP category							
Immaturity	27 (56%)	26 (54%)	23 (41%)	21 (47%)	8 (29%)	12 (32%)	15 (44%)
Hypoxia	9 (19%)	10 (21%)	11 (20%)	8 (18%)	9(32%)	13 (35%)	7 (21%)
Sepsis	9 (19%)	7 (15%)	13 (23%)	10 (22%)	3 (11%)	9 (24%)	10 (29%)
Congenital abnormality	2 (4%)	4 (8%)	7 (13%)	5 (11%)	7 (25%)	3 (8%)	2 (6%)
Sepsis	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (4%)	0	0
Birth weight categories of neonatal deaths							
Inborn:							
<1000g	25 (52%)	18 (38%)	12 (21%)	19 (42%)	5 (18%)	6 (16%)	12 (35%)
1000-1499g	2 (4%)	5 (10%)	8 (14%)	5 (11%)	1 (4%)	7 (19%)	3 (9%)
1500-2499g	4 (8%)	6 (13%)	6 (11%)	2 (4%)	7 (25%)	7 (19%)	4 (12%)
≥2500	5 (10%)	10 (21%)	13 (23%)	9 (20%)	10 (36%)	5 (14%)	3 (9%)
Outborn:							
<1000g	5 (10%)	5 (10%)	9 (16%)	2 (4%)	2 (7%)	3 (8%)	7 (21%)
1000-1499g	2 (4%)	1 (2%)	4 (7%)	1 (2%)	1 (4%)	3 (8%)	2 (6%)
1500-2499g	2 (4%)	3 (6%)	0	3 (7%)	0	4 (11%)	1 (3%)
≥2500	3 (6%)	0	4 (7%)	4 (9%)	2 (7%)	2 (5%)	2 (6%)
Age at death, days: median (IQR)	2 (1 – 4)	2 (1 – 4)	2.5 (1 -5)	1 (0 – 2)	1 (0 – 4)	1 (1 – 5)	1 (1 – 9)
Neonatal death category							
Early NND	41 (85%)	44 (92%)	46 (82%)	40 (89%)	25 (86%)	31 (84%)	24 (71%)
Late NND	7 (15%)	4 (8%)	10 (18%)	5 (11%)	4 (14%)	6 (16%)	10 (29%)
Specific causes of death							
HIE	3 (6%)	6 (13%)	6 (11%)	5 (11%)	6 (21%)	3 (8%)	3 (9%)
MAS/PPHN	5 (10%)	3 (6%)	4 (7%)	2 (4%)	3 (11%)	5 (13%)	3 (9%)
NEC	4 (8%)	3 (6%)	5 (9%)	4 (8%)	0	3 (8%)	0
Congenital syphilis	1 (2%)	1 (2%)	2 (4%)	0	0	0	0
Other sepsis	4 (8%)	3 (6%)	6 (11%)	6 (13%)	3 (11%)	6 (16%)	10 (29%)
HIV exposed	7 (15%)	9 (19%)	15 (27%)	14 (31%)	4 (14%)	15 (41%)	12 (35%)

PPIP: Perinatal Problem Identification Program
NND: Neonatal death
HIE: Hypoxic ischaemic encephalopathy
MAS: Meconium aspiration syndrome
PPHN: Persistent pulmonary hypertension of the newborn
NEC: Necrotising enterocolitis

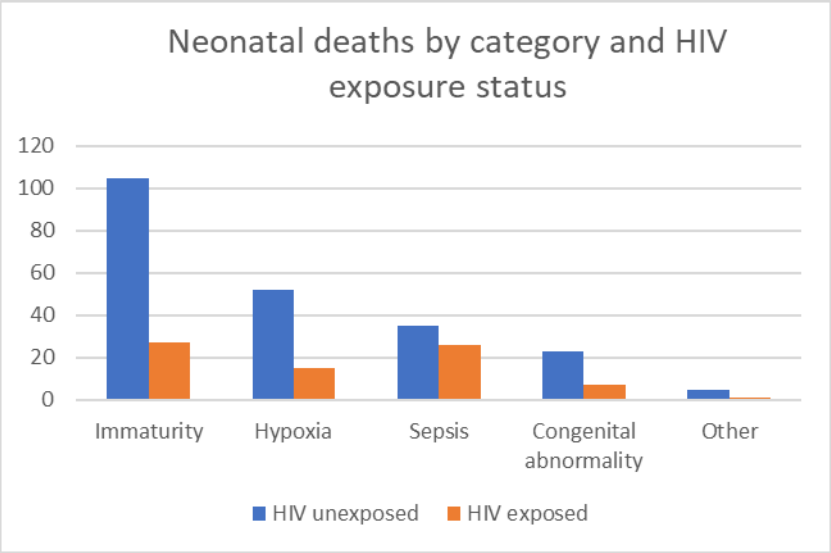
Figure 1: Causes of neonatal deaths, 2011-2018



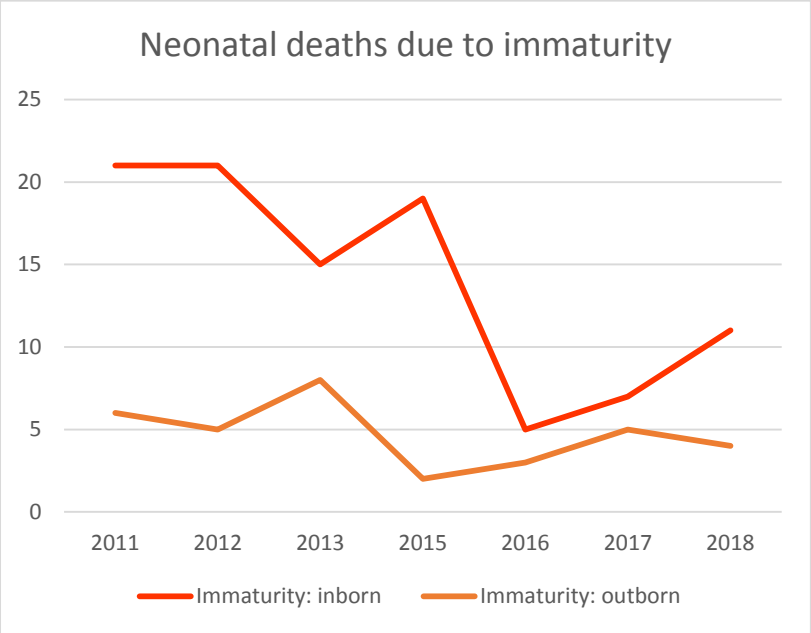
Supplementary table 1: Mean neonatal deaths per month, compared to recorded neonatal deaths in 2014, to illustrate incomplete data for several months

Month	Mean number of deaths per month, 2011-2013 and 2015-2018	Neonatal death, per month, in 2014
January	4.3	2
February	2.7	1
March	4.4	3
April	3.3	0
May	5.9	3
June	2.4	2
July	3.9	0
August	2.6	3
September	2.9	1
October	3.3	2
November	2.3	0
December	4.1	4

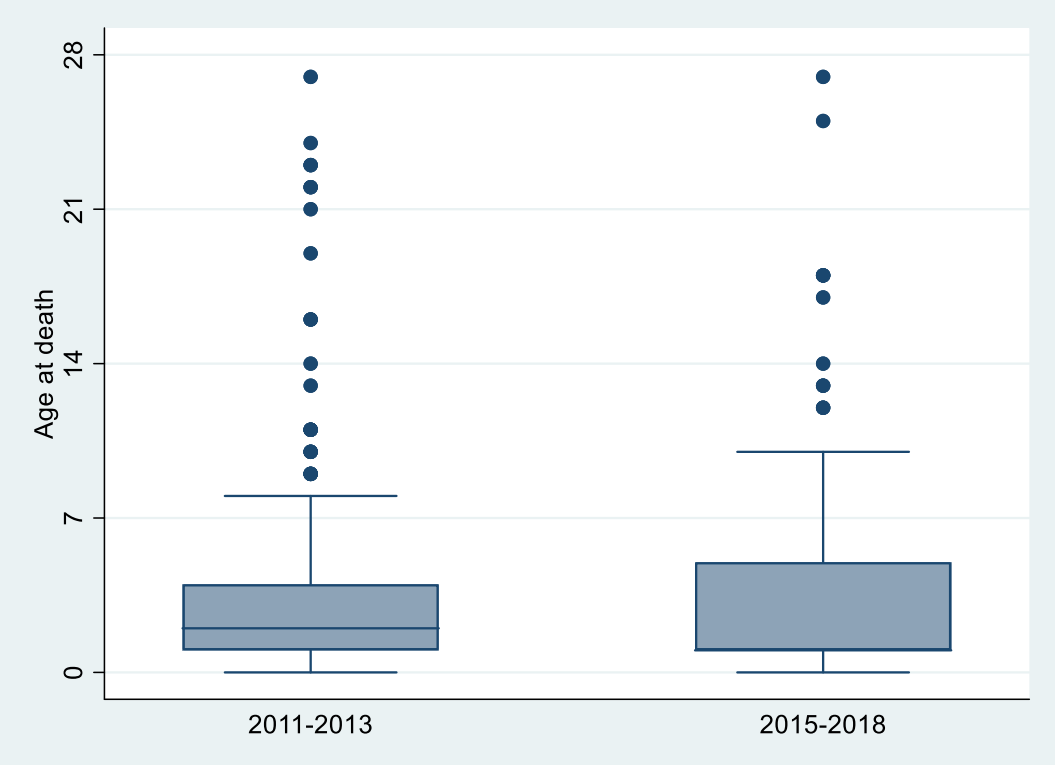
Supplementary figure 1: Causes of death of HIV-exposed and HIV unexposed neonates



Supplementary fig 2: Decreases in numbers of neonatal deaths due to prematurity, by inborn status



Supplementary fig 3: Age at death, before and after implementation of high flow nasal cannula oxygen



In-hospital neonatal mortality in a level-two hospital in Cape Town, South Africa

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Introduction

Neonatal mortality (deaths in the first 28 days of life) has been a major contributor to under-5 mortality in South Africa, accounting for a third of under-5 deaths in 2015.[1] Due to improvements in management of HIV, pneumonia and gastroenteritis,[2] under-5 child mortality in South Africa decreased dramatically over the last 20 years, from a peak of 80 deaths per 1000 live births at the height of the HIV epidemic in 2004[3] to 34 deaths per 1000 live births in 2018.[2] However, neonatal mortality in South Africa has remained static at 11-12 deaths per 1000 live births for nearly 20 years,[2 3] so the relative contribution of neonatal mortality to total under-5 mortality has increased from 14% in 2002 to 32% in 2018.[2] Neonatal mortality must be addressed if South Africa is to meet target 3.2.12 of the Sustainable Development Goals (SDG's) by 2030, namely under-5 child mortality of less than 25 deaths per 1000 live births.[1] ~~? by 2030~~

The leading causes of under-5 mortality in South Africa are prematurity, asphyxia, HIV/AIDS, pneumonia and diarrhoeal diseases;[1 3] neonatal sepsis is also a major contributor to both early (day 1-7) and late (day 8-28) neonatal deaths.[4] Much research into the cause of neonatal deaths in South Africa and potential modifiable factors has been performed. Most pooled neonatal death surveys focus on causes of early neonatal deaths, and late NND's are under-reported.[5 -6] In a retrospective database review of 142

hospitals between October 1999 and September 2003, Velaphi et al described 4502 neonatal deaths. Prematurity accounted for 35% of deaths and 32% of deaths were due to asphyxia-hypoxia.[7] Early continuous positive airway pressure (CPAP)[8] and exogenous surfactant therapy[9] has improved survival of extremely low birth weight neonates (ELBW) in tertiary neonatal units. High flow nasal cannula oxygen (HFNC) has been used for pre-term neonates instead of CPAP with good results.[10] Furthermore, there is evidence that outborn neonates transferred to tertiary neonatal centers have worse outcomes than inborn neonatbabies.[11] or shoul there be a definition of outborn v inborn as an introductory sentence followed by the statement " furthermore"? However ,there is little evidence regarding outcomes of introduction of CPAP and HFNCimpacts of these recent improvements in neonatal care on neonatal mortality outside of tertiary academic centers; , nor of outcomes of outborn neonates who are transferred to non-tertiary neonatal units, where most neonatal care in South Africa is delivered.

For these reasons, we aimed to investigate neonatal mortality in a level 2 neonatal unit in Cape Town, South Africa, over the period when HFNC was introduced, to better understand causes of early and late neonatal mortality; and to analyze inborn vs outborn neonatal mortality. ; and to observe mortality changes over the period when HFNC was introduced.

Methods

New Somerset Hospital (NSH) is a level 2 hospital in Cape Town, South Africa. NSH performs about 6000 deliveries per year, and receives referrals from a wide geographic area, including local urban primary level delivery facilities, and remote rural hospitals up to 200km away. CPAP, surfactant and short-term ventilation (<3 days) are offered; high flow nasal cannula oxygen (HFNC) was introduced in 2015, but long-term ventilation (3 days or more), high-frequency oscillatory ventilation (HFOV), inotropic support, total parenteral nutrition are not available. N; eonates babies children who require escalation of neonatal care are referred to the tertiary hospital, Groote Schuur Hospital (GSH); neonates children requiring surgical intervention are referred to Red Cross War Memorial Children's Hospital (RCWMCH). Neonates born at other facilities and transferred to NSH were considered "outborn".

A database of all neonatal deaths was maintained by the lead consultant in the neonatal unit. Approval to maintain the database was obtained from University of Cape Town (UCT).

Human Research Ethics Committee (HREC Ref 391/2011). The neonatal mortality database included all neonates who died either on-site at New Somerset Hospital, or after transfer to a level 3 facility (GSH or RCWMCH); information about neonatal deaths was captured in real time by doctors (registrars and medical officers) into a file kept in the neonatal high care unit (HCU) should this explanation be mentioned earlier when the word was used?, and entered into a password-protected computerized database (initially an Excel spreadsheet, then an Access database) by the neonatal consultant on a weekly basis. Variables included gestational age, weight, sex, mode of delivery, and HIV exposure status. Early neonatal deaths were submitted to the local coordinators of the Perinatal Problem Identification Program (PPIP).; a structured national project for district-level longitudinal tracking of still births and early neonatal deaths. [4] Deaths were coded according to categories used by the PPIP Perinatal Problem Identification Program (PPIP)[4] for main causes of death (immaturity, hypoxia, sepsis, congenital anomalies and other). Birth weight was considered in the following categories: classified as >=2500g, low birth weight (LBW, 1500g-2499g,), very low birth weight (VLBW, 1000-1499g) and extremely low birth weight (ELBW, and <1000g). Survival status of neonates after transfer to level 3 was determined and entered monthly. The password-protected database was only accessible to the neonatal consultant. An anonymous de-identified subset of data without any personal identifiers was analyzed by the investigators. This analysis was restricted to deaths occurring in the first 28 days of life. Neonatal deaths that occurred in labour ward were excluded, as they were never admitted to the neonatal unit. The study was approved by UCT Human Research Ethics Committee (HREC REF 71/2019). Permission to conduct the study was granted by the chief executive officer of NSH.

Statistical analysis

Categorical variables were compared percentages and proportions, and by chi-squared test; means were compared by t-test. Ceontinuous variables were presented as median and interquartile range (IQR) as they were not normally distributed, and compared with Mann-Whitney U test. Frequency tables, histograms and basic analyses were generated in Microsoft Excel; medians and IQR were calculated in Stata version 16.

Results

Neonatal deaths from 2011 to 2018 were compiled, with the exclusion of 2014, due to incomplete data capturing for several months of that year, supplementary table 1. In the

seven~~7~~ years under review, there were 46 441 births at NSH, and 8166 admissions to the neonatal unit: 6205 (76%) of the neonatal admissions were inborn and 1961 (24%) were transferred in from other birth units. There were 296 neonatal deaths associated with NSH HCU; 219 (74%) were inborn and 77 (26%) were outborn, either born before arrival or transferred in from a level one~~1~~ facility or maternal obstetric unit~~s~~, table 1. Most of the neonatal death~~s~~~~es~~ (221, 75%) occurred died at NSH, but 75 (25%) occurred after transfer to another unit. There were 171 (58%) males. Median birthweight was 1140g (IQR 790 – 2420); nearly half the neonatal deaths (130, 44%) ~~were ELBW, had ?a~~ birth weight <1000g. Median gestation of neonates~~ or babies~~ who died was 29 weeks (IQR 25 – 38), with no significant difference between inborn and outborn (p=0.86). Overall, a majority of neonates (181/296, 61%) who died were delivered by normal vertex delivery (NVD) and were not HIV exposed (220/296, 74%). Median age at death was day 1 (IQR 1-4) for outborn vs day 2 (IQR 1-4) for inborn, p=0.20.

Commented [DIR1]: define

"Immaturity" was the most commonly coded cause of death (132/296, 45%); this category included neonates who had been recorded as having extreme prematurity (94, 32%), hyaline membrane disease (31, 11%) and pre-term intraventricular haemorrhage (7, 2%). "Perinatal hypoxia" included hypoxic ischaemic encephalopathy (32, 11%) and meconium aspiration syndrome (MAS) with or without~~out~~ persistent pulmonary hypertension of the newborn (PPHN) (25, 8%). Perinatal hypoxia was a more common cause of death among inborn neonates (54/219, 25%) compared to outborn neonates (13/77, 17%), but this difference was not statistically significant, p=0.16. Infection-related causes included 19 cases (6%) of necrotizing enterocolitis (NEC), 2 of which had an organism identified (one~~1~~ each of *Serratia marcescens* and *Escherischia coli*) and 17 were culture-negative. There were 38 neonatal deaths due to non-abdominal sepsis; 31/38 (82%) were culture-negative; those with positive cultures included 3 cases of *Pseudomonas aeruginosa*, and one~~1~~ case of each of *Streptococcus agalactiae*, *Candida albicans*, *Enterobacter cloacae*, and a mixed infection of *Klebsiella pneumoniae* and *Acinetobacter baumanii*. There were four~~4~~ (1%) neonatal deaths due to congenital syphilis. Infection-related causes of death were more common among outborn neonates (25/77, 32%) vs inborn neonates (36/219, 16%, p=0.003). Of the 30 neonates dying with congenital abnormalities, there were four~~4~~ with trisomy 18; 12 had multiple anomalies but not a recognizable syndrome; seven~~7~~ had congenital cardiac lesions, two~~2~~ of whom also had trisomy 21; five~~5~~ had pulmonary hypoplasia, and one~~1~~ each with a central nervous system lesion and congenital anaemia. The category of "other" causes of

death included four~~4~~ neonates who had haemorrhages (one~~1~~ subaponeurotic, one~~1~~ intracerebral, two~~2~~ other exsanguinating haemorrhages) and two~~2~~ due to metabolic disorders.

Among neonates of different of birth weight categories, there were differences in method of delivery and cause of death: most ELBW neonatal deaths (107/130, 82%) followed NVD, and immaturity was the main cause of death (104/130, 80%); whereas neonatal deaths with birth weight >2500, hypoxia was the main cause (50/72, 69%) and Caesarean section was the most common delivery method (39/72, 54%), table 1. There were no significant differences in age at death among neonates of different birth weight categories.

Throughout the study period, antenatal HIV prevalence among pregnant women remained constant at about 20%; there were similar numbers of deaths of HIV-exposed neonates in all weight categories, table 1. There was a higher proportion of HIV exposed neonates dying ~~to~~ due to ~~-~~infectious causes (26/61, 43%) compared to other causes (50/235, 21%, p=0.001), Supplementary fig 1.

There was a gradual trend towards decreasing number of neonatal deaths (from 48 in 2011 to 34 in 2018) and rate of deaths (from 45.2 per 1000 admissions to 28.2 per 1000 admissions, table 2). This was largely driven by decreased deaths due to immaturity, from 27 (56%) in 2011 to 15 (44%) in 2018, figure 1; deaths among~~in~~ ELBW decreased from 25 (52%) to 12 (35%), table 2. Number of deaths in other birth weight categories and due to other causal categories remained approximately constant, table 2. Mean number of deaths due to immaturity before 2014 (average 25.3 per year) was significantly less than mean number of deaths after 2014 (average 14.0 per year, p=0.01). The decrease in number of deaths due to immaturity was more marked in neonates who were in inborn (from 21 in 2011 to 11 in 2018) compared to those who were outborn (from six~~6~~ to four~~4~~), supplementary figure 2. There were four~~4~~ deaths due to congenital syphilis prior to 2015 and none after 2015. Age at death after 2015 was lower (median 1 day, IQR 1 – 5) compared to neonates born before 2015 (median 2 days, IQR 1 – 4), supplementary figure 3; but this was not statistically significant, p=0.86.

Discussion

In this retrospective observational study, we observed decreasing numbers of neonatal deaths and decreased neonatal mortality rate among both inborn and outborn neonates; the decrease in number deaths was more marked for deaths due to immaturity than for other cause of death codes. Over the same period of time, neonatal death rate in South Africa remained almost unchanged (between 11 and 12 deaths per 1000 live births~~,~~[2]); in Cape Town (Metro West), early neonatal deaths decreased from 7.6 to 6.4 deaths per 1000 live births.(New Somerset Hospital 2018 PPIP report, Dr Lizel Jacobs, personal communication)

Possible reasons for the observed decrease in neonatal deaths due to immaturity and in neonates in the lowest birth weight category through the course of the study period may be due to changes in policy regarding respiratory support for preterm neonates. Prior to 2015, neonates needing respiratory support received low-flow, non-humidified, blended oxygen. Limited CPAP machines were available for neonates weighing >1000g and if gestation was at least 28 weeks. From 2015, warmed humified blended high flow nasal cannula oxygen was available for all neonates, irrespective of weight or gestational age. From 2017, CPAP and surfactant were made available to neonates with birth weight >800g if gestational age was at least 28 weeks. High flow nasal cannula (HFNC) oxygen therapy in preterm infants has been associated with similar outcomes to nasal continuous airway pressure (CPAP) with fewer complications and less nasal trauma.[12] It is possible that the introduction of early HFNC in 2015 was associated with improved survival of preterm inborn neonates. The reason that deaths of outborn preterm neonates did not decrease to the same extent as inborn preterm neonates may be due to delays in transport from other facilities; neonates may have spent many hours receiving unheated non-humidified oxygen before admission to NSH, which may have caused hypothermia, atelectasis and lung inflammation.[11] Outborn neonates were also more likely to die of infectious-related causes: it is possible that potential improvements in respiratory care were mitigated by ongoing high risk of exposure to infection while in transit to NSH. It is difficult to see from this data whether decreasing the threshold to qualify for CPAP and surfactant ~~form~~in 2017 had any further impact on neonatal mortality. There had been ~~was~~ some concern that introduction of HFNC in 2014 ~~or 2015~~may prolong survival of ELBW neonates beyond day 7, but that most of these neonates would subsequently die of NEC or sepsis. However, since we did not observe an increase in late deaths from other causes, and ~~that~~ the age at death did not change throughout the study period, we believe that the observed decrease in early deaths due to immaturity is real, and is not simply due to shifting the mortality burden into a different category. There was some

turnover in doctors working in the unit, but there was low turnover of nursing staff; there were no other major changes in practice or policy regarding management of perinatal hypoxia, suspected sepsis or other neonatal conditions during~~over~~ the period under review.

The number of deaths due to hypoxia did not change much over the study period. Throughout the study period, NSH neonatal unit practiced therapeutic hypothermia for moderate / severe hypoxic ischaemic encephalopathy, and used amplitude-integrated electroencephalograms to monitor cerebral function in neonates with brain injury. However, addressing deaths due to perinatal hypoxia will require obstetric interventions and labour ward management; improved neonatal care will not be sufficient to substantially reduce hypoxia-related deaths.[13] There were ~~more~~ relatively more deaths due to hypoxia among inborn neonates compared to those referred in from other facilities. It is likely that the most severely brain injured neonates who were born at other facilities demised within a few hours of life, before the ambulance transport could bring them to NSH.

The striking decrease in hospital-related neonatal deaths has not been seen in the annual PPIP reports. There are a number of reasons for this. PPIP reports early NND's according to the delivery unit, and includes all neonates who die in labour ward or after admission to a neonatal unit. In this analysis, as we were only considering in-hospital mortality of the neonatal unit, we excluded all labour-ward deaths, but we included outborn neonates~~babies~~ who were admitted to our unit if they subsequently died~~ in our unit.~~ For this reason, PPIP stats are a more sensitive longitudinal indicator of trends for delivery units and labour wards; the current analysis is better suited to detect trends in survival that are affected by changes in neonatal practice, not labour ward management.

There was a low rate of blood culture positivity among neonates who were attributed an "infection-related" cause of death. Although the unit policy is to always draw a blood culture before starting or escalating antibiotics, it is possible that some critically ill neonates may have died before cultures could be drawn, or that inadequate blood volumes were drawn,[14] and this resulted in low culture positivity; or that true pathogen growth was masked by skin contaminants.[15] It is also possible that some of neonatal deaths labelled as "infection-related" may have been misclassified: neonates who had a clinical deterioration and demised may actually have had underlying cardiac or metabolic disease that was not diagnosed.

There is good evidence that both HIV-infected and HIV-exposed uninfected (HEU) infants have higher rates of infectious morbidity than HIV-unexposed infants.[16 17] However the higher proportion of infection-related deaths among HIV-exposed neonates is difficult to interpret, as most neonates did not have nucleic-acid testing at the time of death. Universal antiretroviral therapy for pregnant women for prevention of mother to child transmission of HIV (PMTCT) was introduced in 2013[18] but universal birth PCR testing was only introduced in 2015;[19] it is possible that some considered to be "HIV exposed" were actually *in utero* HIV infected, and already had profound immune compromise at the time of death.

There are a number of important limitations with this data analysis. This was a retrospective review of an existing database, therefore no patient folders were reviewed or interrogated regarding possible adverse outcomes. We accepted the clinical judgement of the attending clinician at the time the data were captured regarding the likely cause and category of death. However, misclassification of causes of death is possible, as very few autopsies were performed. As mentioned above, cardiac or metabolic diseases may have been misclassified as "infection-related" deaths. Annual total numbers of births in labour ward and admissions to the neonatal unit were available; however as this was not disaggregated by birth weight categories, it is not possible to calculate a neonatal mortality rate per birth weight category as the denominator for each birth weight category is not known. It would have been valuable to ~~be able to~~ calculate early and late neonatal death rates by weight category, to observe if any changes occurred during the period under review. Data collection in 2014 was obviously incomplete: for 11 months of that year the number of deaths were far below the mean number of deaths for the rest of the study period, and there were three ~~there were many~~ months with no deaths recorded at all. I~~; it~~t would have been inappropriate to include that year. ~~was easier to exclude that year altogether.~~ However it is possible that some deaths were missed and not entered into the database: the same paediatrician supervised the unit from the end of 2014 till 2018, and the same data capture systems were in place; but with a manual system of data capture and data entry, it is possible that some deaths may have been missed. PPIP does not capture access to neonatal therapies (HFNC, CPAP, surfactant, therapeutic hypothermia): it was not possible to compare impact of neonatal therapies within the neonatal unit over time as this data was not available.

Conclusion

In this retrospective analysis of an existing database, we observed decreasing number of neonatal deaths over the period 2011-2018; the category with the largest decrease was inborn deaths due to prematurity, while all other numbers of deaths due to all other causes remained approximately the same. This period coincided with the introduction of high flow nasal cannula oxygen into the neonatal unit, and subsequent expansion of CPAP eligibility criteria from 1000g to 800g. These advances in respiratory support may have contributed to some of the observed decreased deaths due to prematurity. Combinations of interventions may be required to reduce the residual burden of neonatal mortality in South Africa. Expansion of access to HFNC and CPAP may reduce deaths due to prematurity, but other upstream interventions, including improved access to antenatal care (like steroids for preterm labour) and other obstetric interventions in labour ward, will be required to address the residual burden of immaturity- and hypoxia-related causes of neonatal mortality.

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Neonatal mortality_tables and figures

Table 1: Characteristics of neonatal deaths by birth weight category

	Birthweight <1000g N=130	Birthweight 1000-1499g N=45	Birthweight 1500-2499g N=49	Birthweight ≥2500 N=72	Total N=296
Place born:					
Inborn	97 (75%)	31 (69%)	36 (73%)	55 (76%)	219 (74%)
BBA	14 (11%)	7 (16%)	3 (6%)	4 (6%)	28 (9%)
Vanguard MOU	6 (5%)	2 (4%)	5 (10%)	4 (6%)	17 (6%)
Vredenburg Hospital	6 (5%)	1 (2%)	2 (4%)	6 (7%)	14 (5%)
Wesfleur Hospital	4 (3%)	2 (4%)	0	2 (3%)	8 (3%)
Other	3 (2%)	2 (4%)	3 (6%)	2 (3%)	10 (3%)
Place died					
NSH	127 (98%)	25 (55%)	28 (57%)	41 (57%)	221 (75%)
RCWMCH	0	3 (7%)	6 (12%)	2 (3%)	11 (4%)
GSH	3 (2%)	16 (36%)	14 (29%)	29 (40%)	62 (21%)
Other	0	1 (2%)	1 (2%)	0	1 (0.7%)
Male sex	78 (60%)	25 (56%)	28 (57%)	40 (56%)	171 (58%)
HIV exposure status					
Unexposed	97 (75%)	31 (69%)	36 (73%)	36 (73%)	220 (74%)
Exposed	33 (25%)	14 (31%)	13 (27%)	16 (22%)	76 (26%)
Delivery method					
Normal vertex delivery	107 (82%)	20 (44%)	26 (53%)	28 (39%)	181 (61%)
Caesarean section	11 (8%)	23 (51%)	21 (43%)	39 (54%)	94 (32%)
Vaginal breech	12 (9%)	2 (4%)	1 (2%)	1 (1%)	16 (5%)
Forceps	0	0	0	4 (6%)	4 (1%)
Vacuum	0	0	1 (2%)	0	1 (0.3%)
Cause of death by PPIP category					
Immaturity	104 (80%)	24 (53)	4 (8%)	0	132 (45%)
Hypoxia	0	4 (9%)	13 (27%)	50 (69%)	67 (23%)
Infection	25 (19%)	15 (33%)	14 (29%)	7 (10%)	61 (21%)
Congenital anomaly	1 (1%)	2 (4%)	17 (35%)	10 (14%)	30 (10%)
Other	0	0	1 (2%)	5 (7%)	6 (2%)
Age at death, days: median (IQR)	1 (0 – 4)	2 (1 – 6)	2 (1 – 5)	2 (1 – 3)	1 (1 – 4)
Neonatal death category					
Early NND	108 (83%)	35 (78%)	41 (84%)	66 (92%)	250 (84%)
Late NND	22 (17%)	10 (22%)	8 (16%)	6 (8%)	46 (17%)

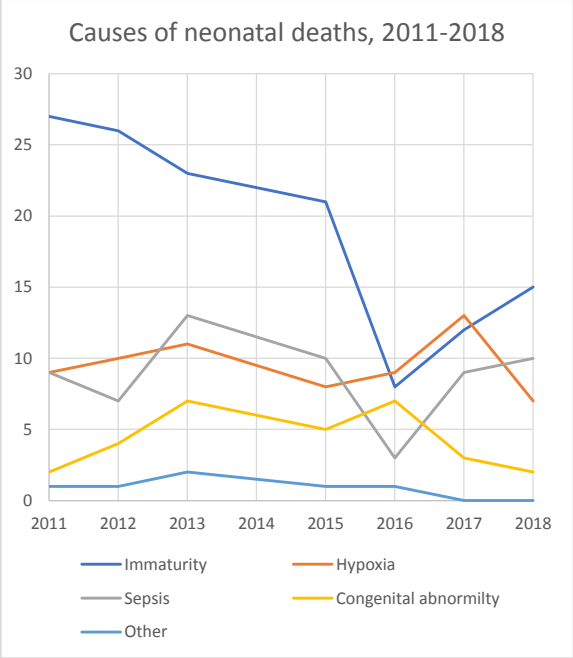
BBA: Born before arrival
MOU: Midwife obstetric unit
NSH: Nnew Somerset Hospital
GSH: Groote Schuur Hospital
RCWMCH: Red Cross War Memorial Children's Hospital
PPIP: Perinatal Problem Identification Program
NND: Neonatal death

Table 2: Neonatal deaths per year of study

	2011 N=48	2012 N=48	2013 N=56	2015 N=45	2016 N=28	2017 N=37	2018 N=34
Rate of neonatal deaths, per 1000 admissions							
All	45.2	44.6	38.3	38.6	27.3	31.6	28.2
Inborn	44.9	47.1	34.6	41.2	30.6	29.2	22.5
Outborn	49.1	36.4	50.6	31.6	18.3	38.2	52.4
Causes of death by PPIP category							
Immaturity	27 (56%)	26 (54%)	23 (41%)	21 (47%)	8 (29%)	12 (32%)	15 (44%)
Hypoxia	9 (19%)	10 (21%)	11 (20%)	8 (18%)	9(32%)	13 (35%)	7 (21%)
Sepsis	9 (19%)	7 (15%)	13 (23%)	10 (22%)	3 (11%)	9 (24%)	10 (29%)
Congenital abnormality	2 (4%)	4 (8%)	7 (13%)	5 (11%)	7 (25%)	3 (8%)	2 (6%)
Sepsis	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (4%)	0	0
Birth weight categories of neonatal deaths							
Inborn:							
<1000g	25 (52%)	18 (38%)	12 (21%)	19 (42%)	5 (18%)	6 (16%)	12 (35%)
1000-1499g	2 (4%)	5 (10%)	8 (14%)	5 (11%)	1 (4%)	7 (19%)	3 (9%)
1500-2499g	4 (8%)	6 (13%)	6 (11%)	2 (4%)	7 (25%)	7 (19%)	4 (12%)
≥2500	5 (10%)	10 (21%)	13 (23%)	9 (20%)	10 (36%)	5 (14%)	3 (9%)
Outborn:							
<1000g	5 (10%)	5 (10%)	9 (16%)	2 (4%)	2 (7%)	3 (8%)	7 (21%)
1000-1499g	2 (4%)	1 (2%)	4 (7%)	1 (2%)	1 (4%)	3 (8%)	2 (6%)
1500-2499g	2 (4%)	3 (6%)	0	3 (7%)	0	4 (11%)	1 (3%)
≥2500	3 (6%)	0	4 (7%)	4 (9%)	2 (7%)	2 (5%)	2 (6%)
Age at death, days: median (IQR)	2 (1 – 4)	2 (1 – 4)	2.5 (1 -5)	1 (0 – 2)	1 (0 – 4)	1 (1 – 5)	1 (1 – 9)
Neonatal death category							
Early NND	41 (85%)	44 (92%)	46 (82%)	40 (89%)	25 (86%)	31 (84%)	24 (71%)
Late NND	7 (15%)	4 (8%)	10 (18%)	5 (11%)	4 (14%)	6 (16%)	10 (29%)
Specific causes of death							
HIE	3 (6%)	6 (13%)	6 (11%)	5 (11%)	6 (21%)	3 (8%)	3 (9%)
MAS/PPHN	5 (10%)	3 (6%)	4 (7%)	2 (4%)	3 (11%)	5 (13%)	3 (9%)
NEC	4 (8%)	3 (6%)	5 (9%)	4 (8%)	0	3 (8%)	0
Congenital syphilis	1 (2%)	1 (2%)	2 (4%)	0	0	0	0
Other sepsis	4 (8%)	3 (6%)	6 (11%)	6 (13%)	3 (11%)	6 (16%)	10 (29%)
HIV exposed	7 (15%)	9 (19%)	15 (27%)	14 (31%)	4 (14%)	15 (41%)	12 (35%)

PPIP: Perinatal Problem Identification Program
NND: Neonatal death
HIE: Hypoxic ischaemic encephalopathy
MAS: Meconium aspiration syndrome
PPHN: Persistent pulmonary hypertension of the newborn
NEC: Necrotising enterocolitis

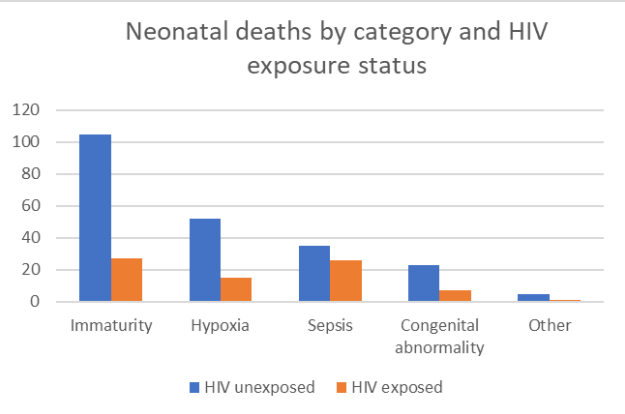
Figure 1: Causes of neonatal deaths, 2011-2018



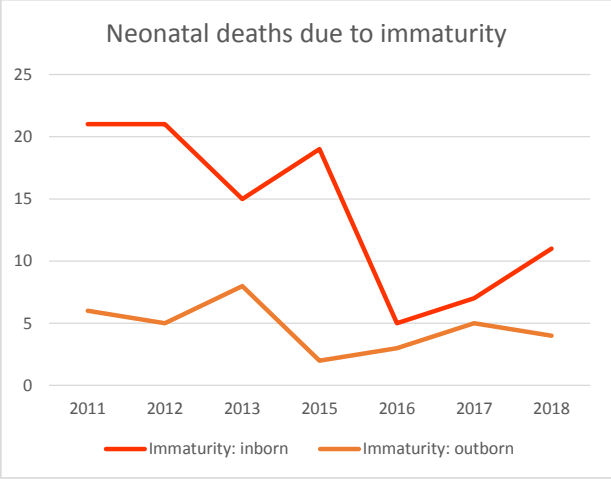
Supplementary table 1: Mean neonatal deaths per month, compared to recorded neonatal deaths in 2014, to illustrate incomplete data for several months

Month	Mean number of deaths per month, 2011-2013 and 2015-2018	Neonatal death, per month, in 2014
January	4.3	2
February	2.7	1
March	4.4	3
April	3.3	0
May	5.9	3
June	2.4	2
July	3.9	0
August	2.6	3
September	2.9	1
October	3.3	2
November	2.3	0
December	4.1	4

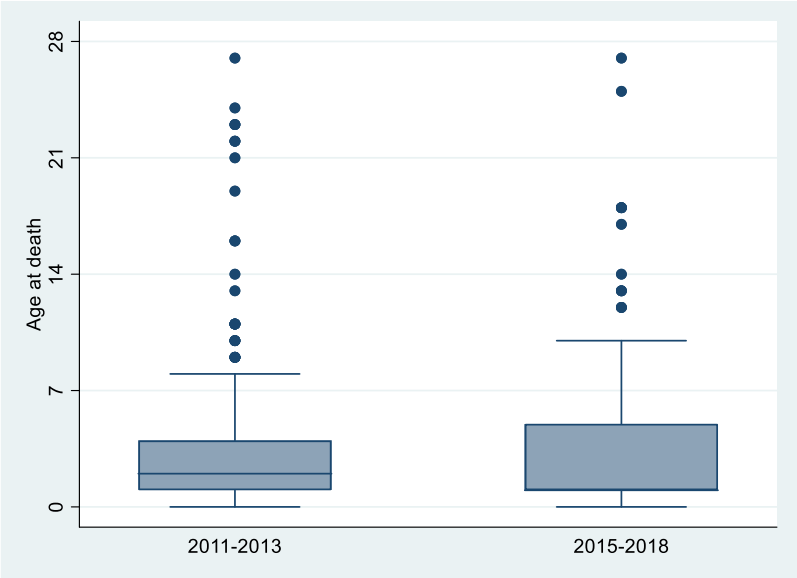
Supplementary figure 1: Causes of death of HIV-exposed and HIV unexposed neonates



Supplementary fig 2: Decreases in numbers of neonatal deaths due to prematurity, by inborn status



Supplementary fig 3: Age at death, before and after implementation of high flow nasal cannula oxygen



In-hospital neonatal mortality in a level-two hospital in Cape Town, South Africa

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Introduction

Neonatal mortality (deaths in the first 28 days of life) has been a major contributor to under-5 mortality in South Africa, accounting for a third of under-5 deaths in 2015.[1] Due to improvements in management of HIV, pneumonia and gastroenteritis,[2] under-5 child mortality in South Africa decreased dramatically over the last 20 years, from a peak of 80 deaths per 1000 live births at the height of the HIV epidemic in 2004[3] to 34 deaths per 1000 live births in 2018.[2] However, neonatal mortality in South Africa has remained static at 11-12 deaths per 1000 live births for nearly 20 years,[2 3] so the relative contribution of neonatal mortality to total under-5 mortality has increased from 14% in 2002 to 32% in 2018.[2] Neonatal mortality must be addressed if South Africa is to meet target 3.2.1 of the Sustainable Development Goals (SDG's) by 2030, namely under-5 child mortality of less than 25 deaths per 1000 live births.[1]

The leading causes of under-5 mortality in South Africa are prematurity, asphyxia, HIV/AIDS, pneumonia and diarrhoeal diseases;[1 3] neonatal sepsis is also a major contributor to both early (day 1-7) and late (day 8-28) neonatal deaths.[4] Much research into the cause of neonatal deaths in South Africa and potential modifiable factors has been performed. Most pooled neonatal death surveys focus on causes of early neonatal deaths,

and late NND's are under-reported.[5 -6] In a retrospective database review of 142 hospitals between October 1999 and September 2003, Velaphi et al described 4502 neonatal deaths. Prematurity accounted for 35% of deaths and 32% of deaths were due to asphyxia-hypoxia.[7] Early continuous positive airway pressure (CPAP)[8] and exogenous surfactant therapy[9] has improved survival of extremely low birth weight neonates (ELBW) in tertiary neonatal units. High flow nasal cannula oxygen (HFNC) has been used for pre-term neonates instead of CPAP with good results.[10] Furthermore, there is evidence that outborn neonates transferred to tertiary neonatal centers have worse outcomes than inborn neonates.[11] However there is little evidence regarding impacts of these recent improvements in neonatal care on neonatal mortality outside of tertiary academic centers; nor of outcomes of outborn neonates who are transferred to non-tertiary neonatal units, where most neonatal care in South Africa is delivered.

For these reasons, we aimed to investigate neonatal mortality in a level 2 neonatal unit in Cape Town, South Africa, to better understand causes of early and late neonatal mortality; and to analyze inborn vs outborn neonatal mortality.

Methods

New Somerset Hospital (NSH) is a level 2 hospital in Cape Town, South Africa. NSH performs about 6000 deliveries per year, and receives referrals from a wide geographic area, including local urban primary level delivery facilities, and remote rural hospitals up to 200km away. CPAP, surfactant and short-term ventilation (<3 days) are offered; high flow nasal cannula oxygen (HFNC) was introduced in 2015, but long-term ventilation (3 days or more), high-frequency oscillatory ventilation (HFOV), inotropic support, total parenteral nutrition are not available. Neonates who require escalation of neonatal care are referred to the tertiary hospital, Groote Schuur Hospital (GSH); neonates requiring surgical intervention are referred to Red Cross War Memorial Children's Hospital (RCWMCH). Neonates born at other facilities and transferred to NSH were considered "outborn".

A database of all neonatal deaths was maintained by the lead consultant in the neonatal unit. Approval to maintain the database was obtained from University of Cape Town (UCT). Human Research Ethics Committee (HREC Ref 391/2011). The neonatal mortality database included all neonates who died either on-site at New Somerset Hospital, or after transfer to a level 3 facility (GSH or RCWMCH); information about neonatal deaths was

captured in real time by doctors (registrars and medical officers) into a file kept in the neonatal high care unit (HCU), and entered into a password-protected database (initially an Excel spreadsheet, then an Access database) by the neonatal consultant on a weekly basis. Variables included gestational age, weight, sex, mode of delivery, and HIV exposure status. Early neonatal deaths were submitted to the local coordinators of the Perinatal Problem Identification Program (PPIP), a structured national project for district-level longitudinal tracking of still births and early neonatal deaths. [4] Deaths were coded according to categories used by the PPIP for main causes of death (immaturity, hypoxia, sepsis, congenital anomalies and other). Birth weight was considered in the following categories: >=2500g, 1500-2499g, 1000-1499g and <1000g. Survival status of neonates after transfer to level 3 was determined and entered monthly. An anonymous de-identified subset of data without any personal identifiers was analyzed by the investigators. This analysis was restricted to deaths occurring in the first 28 days of life. Neonatal deaths that occurred in labour ward were excluded, as they were never admitted to the neonatal unit. The study was approved by UCT Human Research Ethics Committee (HREC REF 71/2019). Permission to conduct the study was granted by the chief executive officer of NSH.

Statistical analysis

Categorical variables were compared percentages and proportions, and by chi-squared test; means were compared by t-test. Continuous variables were presented as median and interquartile range (IQR) as they were not normally distributed, and compared with Mann-Whitney U test. Frequency tables, histograms and basic analyses were generated in Microsoft Excel; medians and IQR were calculated in Stata version 16.

Results

Neonatal deaths from 2011 to 2018 were compiled, with the exclusion of 2014, due to incomplete data capturing for several months of that year, supplementary table 1. In the seven years under review, there were 46 441 births at NSH, and 8166 admissions to the neonatal unit: 6205 (76%) of the neonatal admissions were inborn and 1961 (24%) were transferred in from other birth units. There were 296 neonatal deaths associated with NSH HCU; 219 (74%) were inborn and 77 (26%) were outborn, either born before arrival or transferred in from a level one facility or maternal obstetric unit, table 1. Most of the neonatal deaths (221, 75%) occurred died at NSH, but 75 (25%) occurred after transfer to another unit. There were 171 (58%) males. Median birthweight was 1140g (IQR 790 –

2420); nearly half the neonatal deaths (130, 44%) had birth weight <1000g. Median gestation of neonates who died was 29 weeks (IQR 25 – 38), with no significant difference between inborn and outborn (p=0.86). Overall, a majority of neonates (181/296, 61%) who died were delivered by normal vertex delivery (NVD) and were not HIV exposed (220/296, 74%). Median age at death was day 1 (IQR 1-4) for outborn vs day 2 (IQR 1-4) for inborn, p=0.20.

"Immaturity" was the most commonly coded cause of death (132/296, 45%); this category included neonates who had been recorded as having extreme prematurity (94, 32%), hyaline membrane disease (31, 11%) and pre-term intraventricular haemorrhage (7, 2%). "Perinatal hypoxia" included hypoxic ischaemic encephalopathy (32, 11%) and meconium aspiration syndrome (MAS) with or without persistent pulmonary hypertension of the newborn (PPHN) (25, 8%). Perinatal hypoxia was a more common cause of death among inborn neonates (54/219, 25%) compared to outborn neonates (13/77, 17%), but this difference was not statistically significant, p=0.16. Infection-related causes included 19 cases (6%) of necrotizing enterocolitis (NEC), 2 of which had an organism identified (one each of *Serratia marcescens* and *Escherischia coli*) and 17 were culture-negative. There were 38 neonatal deaths due to non-abdominal sepsis; 31/38 (82%) were culture-negative; those with positive cultures included 3 cases of *Pseudomonas aeruginosa*, and one case of each of *Streptococcus agalactiae*, *Candida albicans*, *Enterobacter cloacae*, and a mixed infection of *Klebsiella pneumoniae* and *Acinetobacter baumanii*. There were four (1%) neonatal deaths due to congenital syphilis. Infection-related causes of death were more common among outborn neonates (25/77, 32%) vs inborn neonates (36/219, 16%, p=0.003). Of the 30 neonates dying with congenital abnormalities, there were four with trisomy 18; 12 had multiple anomalies but not a recognizable syndrome; seven had congenital cardiac lesions, two of whom also had trisomy 21; five had pulmonary hypoplasia, and one each with a central nervous system lesion and congenital anaemia. The category of "other" causes of death included four neonates who had haemorrhages (one subaponeurotic, one intracerebral, two other exsanguinating haemorrhages) and two due to metabolic disorders.

Among neonates of different of birth weight categories, there were differences in method of delivery and cause of death: most ELBW neonatal deaths (107/130, 82%) followed NVD, and immaturity was the main cause of death (104/130, 80%); whereas neonatal deaths with birth weight >2500, hypoxia was the main cause (50/72, 69%) and Caesarean section was

the most common delivery method (39/72, 54%), table 1. There were no significant differences in age at death among neonates of different birth weight categories.

Throughout the study period, antenatal HIV prevalence among pregnant women remained constant at about 20%; there were similar numbers of deaths of HIV-exposed neonates in all weight categories, table 1. There was a higher proportion of HIV exposed neonates dying due to infectious causes (26/61, 43%) compared to other causes (50/235, 21%, p=0.001), Supplementary fig 1.

There was a gradual trend towards decreasing number of neonatal deaths (from 48 in 2011 to 34 in 2018) and rate of deaths (from 45.2 per 1000 admissions to 28.2 per 1000 admissions, table 2). This was largely driven by decreased deaths due to immaturity, from 27 (56%) in 2011 to 15 (44%) in 2018, figure 1; deaths among ELBW decreased from 25 (52%) to 12 (35%), table 2. Number of deaths in other birth weight categories and due to other causal categories remained approximately constant, table 2. Mean number of deaths due to immaturity before 2014 (average 25.3 per year) was significantly less than mean number of deaths after 2014 (average 14.0 per year, p=0.01). The decrease in number of deaths due to immaturity was more marked in neonates who were in inborn (from 21 in 2011 to 11 in 2018) compared to those who were outborn (from six to four), supplementary figure 2. There were four deaths due to congenital syphilis prior to 2015 and none after 2015. Age at death after 2015 was lower (median 1 day, IQR 1 – 5) compared to neonates born before 2015 (median 2 days, IQR 1 – 4), supplementary figure 3; but this was not statistically significant, p=0.86.

Discussion

In this retrospective observational study, we observed decreasing numbers of neonatal deaths and decreased neonatal mortality rate among both inborn and outborn neonates; the decrease in number deaths was more marked for deaths due to immaturity than for other cause of death codes. Over the same period of time, neonatal death rate in South Africa remained almost unchanged (between 11 and 12 deaths per 1000 live births[2]); in Cape Town (Metro West), early neonatal deaths decreased from 7.6 to 6.4 deaths per 1000 live births.(New Somerset Hospital 2018 PPIP report, Dr Lizel Jacobs, personal communication)

Possible reasons for the observed decrease in neonatal deaths due to immaturity and in neonates in the lowest birth weight category through the course of the study period may be due to changes in policy regarding respiratory support for preterm neonates. Prior to 2015, neonates needing respiratory support received low-flow, non-humidified, blended oxygen. Limited CPAP machines were available for neonates weighing >1000g and if gestation was at least 28 weeks. From 2015, warmed humified blended high flow nasal cannula oxygen was available for all neonates, irrespective of weight or gestational age. From 2017, CPAP and surfactant were made available to neonates with birth weight >800g if gestational age was at least 28 weeks. High flow nasal cannula (HFNC) oxygen therapy in preterm infants has been associated with similar outcomes to nasal continuous airway pressure (CPAP) with fewer complications and less nasal trauma.[12] It is possible that the introduction of early HFNC in 2015 was associated with improved survival of preterm inborn neonates. The reason that deaths of outborn preterm neonates did not decrease to the same extent as inborn preterm neonates may be due to delays in transport from other facilities; neonates may have spent many hours receiving unheated non-humidified oxygen before admission to NSH, which may have caused hypothermia, atelectasis and lung inflammation.[11] Outborn neonates were also more likely to die of infectious-related causes: it is possible that potential improvements in respiratory care were mitigated by ongoing high risk of exposure to infection while in transit to NSH. It is difficult to see from this data whether decreasing the threshold to qualify for CPAP and surfactant in 2017 had any further impact on neonatal mortality. There had been some concern that introduction of HFNC in 2014 may prolong survival of ELBW neonates beyond day 7, but that most of these neonates would subsequently die of NEC or sepsis. However, since we did not observe an increase in late deaths from other causes, and the age at death did not change throughout the study period, we believe that the observed decrease in early deaths due to immaturity is real, and is not simply due to shifting the mortality burden into a different category. There was some turnover in doctors working in the unit, but there was low turnover of nursing staff; there were no other major changes in practice or policy regarding management of perinatal hypoxia, suspected sepsis or other neonatal conditions during the period under review.

The number of deaths due to hypoxia did not change much over the study period. Throughout the study period, NSH neonatal unit practiced therapeutic hypothermia for moderate / severe hypoxic ischaemic encephalopathy, and used amplitude-integrated electroencephalograms to monitor cerebral function in neonates with brain injury. However,

addressing deaths due to perinatal hypoxia will require obstetric interventions and labour ward management; improved neonatal care will not be sufficient to substantially reduce hypoxia-related deaths.[13] There were relatively more deaths due to hypoxia among inborn neonates compared to those referred in from other facilities. It is likely that the most severely brain injured neonates who were born at other facilities demised within a few hours of life, before the ambulance transport could bring them to NSH.

The striking decrease in hospital-related neonatal deaths has not been seen in the annual PPIP reports. There are a number of reasons for this. PPIP reports early NND's according to the delivery unit, and includes all neonates who die in labour ward or after admission to a neonatal unit. In this analysis, as we were only considering in-hospital mortality of the neonatal unit, we excluded all labour-ward deaths, but we included outborn neonates who were admitted to our unit if they subsequently died. For this reason, PPIP stats are a more sensitive longitudinal indicator of trends for delivery units and labour wards; the current analysis is better suited to detect trends in survival that are affected by changes in neonatal practice, not labour ward management.

There was a low rate of blood culture positivity among neonates who were attributed an "infection-related" cause of death. Although the unit policy is to always draw a blood culture before starting or escalating antibiotics, it is possible that some critically ill neonates may have died before cultures could be drawn, or that inadequate blood volumes were drawn,[14] and this resulted in low culture positivity; or that true pathogen growth was masked by skin contaminants.[15] It is also possible that some of neonatal deaths labelled as "infection-related" may have been misclassified: neonates who had a clinical deterioration and demised may actually have had underlying cardiac or metabolic disease that was not diagnosed.

There is good evidence that both HIV-infected and HIV-exposed uninfected (HEU) infants have higher rates of infectious morbidity than HIV-unexposed infants.[16 17] However the higher proportion of infection-related deaths among HIV-exposed neonates is difficult to interpret, as most neonates did not have nucleic-acid testing at the time of death. Universal antiretroviral therapy for pregnant women for prevention of mother to child transmission of HIV (PMTCT) was introduced in 2013[18] but universal birth PCR testing was only introduced in 2015;[19] it is possible that some considered to be "HIV exposed" were

actually *in utero* HIV infected, and already had profound immune compromise at the time of death.

There are a number of important limitations with this data analysis. This was a retrospective review of an existing database, therefore no patient folders were reviewed or interrogated regarding possible adverse outcomes. We accepted the clinical judgement of the attending clinician at the time the data were captured regarding the likely cause and category of death. However, misclassification of causes of death is possible, as very few autopsies were performed. As mentioned above, cardiac or metabolic diseases may have been misclassified as "infection-related" deaths. Annual total numbers of births in labour ward and admissions to the neonatal unit were available; however as this was not disaggregated by birth weight categories, it is not possible to calculate a neonatal mortality rate per birth weight category as the denominator for each birth weight category is not known. It would have been valuable to calculate early and late neonatal death rates by weight category, to observe if any changes occurred during the period under review. Data collection in 2014 was obviously incomplete: for 11 months of that year the number of deaths were far below the mean number of deaths for the rest of the study period, and there were three months with no deaths recorded at all. It would have been inappropriate to include that year. However it is possible that some deaths were missed and not entered into the database: the same paediatrician supervised the unit from the end of 2014 till 2018, and the same data capture systems were in place; but with a manual system of data capture and data entry, it is possible that some deaths may have been missed. PPIP does not capture access to neonatal therapies (HFNC, CPAP, surfactant, therapeutic hypothermia): it was not possible to compare impact of neonatal therapies within the neonatal unit over time as this data was not available.

Conclusion

In this retrospective analysis of an existing database, we observed decreasing number of neonatal deaths over the period 2011-2018; the category with the largest decrease was inborn deaths due to prematurity, while all other numbers of deaths due to all other causes remained approximately the same. This period coincided with the introduction of high flow nasal cannula oxygen into the neonatal unit, and subsequent expansion of CPAP eligibility criteria from 1000g to 800g. These advances in respiratory support may have contributed to some of the observed decreased deaths due to prematurity. Combinations of interventions may be required to reduce the residual burden of neonatal mortality in South Africa.

Expansion of access to HFNC and CPAP may reduce deaths due to prematurity, but other upstream interventions, including improved access to antenatal care (like steroids for preterm labour) and other obstetric interventions in labour ward, will be required to address the residual burden of immaturity- and hypoxia-related causes of neonatal mortality.

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Neonatal mortality_tables and figures

Table 1: Characteristics of neonatal deaths by birth weight category

	Birthweight <1000g N=130	Birthweight 1000-1499g N=45	Birthweight 1500-2499g N=49	Birthweight ≥2500 N=72	Total N=296
Place born:					
Inborn	97 (75%)	31 (69%)	36 (73%)	55 (76%)	219 (74%)
BBA	14 (11%)	7 (16%)	3 (6%)	4 (6%)	28 (9%)
Vanguard MOU	6 (5%)	2 (4%)	5 (10%)	4 (6%)	17 (6%)
Vredenburg Hospital	6 (5%)	1 (2%)	2 (4%)	6 (7%)	14 (5%)
Wesfleur Hospital	4 (3%)	2 (4%)	0	2 (3%)	8 (3%)
Other	3 (2%)	2 (4%)	3 (6%)	2 (3%)	10 (3%)
Place died					
NSH	127 (98%)	25 (55%)	28 (57%)	41 (57%)	221 (75%)
RCWMCH	0	3 (7%)	6 (12%)	2 (3%)	11 (4%)
GSH	3 (2%)	16 (36%)	14 (29%)	29 (40%)	62 (21%)
Other	0	1 (2%)	1 (2%)	0	1 (0.7%)
Male sex	78 (60%)	25 (56%)	28 (57%)	40 (56%)	171 (58%)
HIV exposure status					
Unexposed	97 (75%)	31 (69%)	36 (73%)	36 (73%)	220 (74%)
Exposed	33 (25%)	14 (31%)	13 (27%)	16 (22%)	76 (26%)
Delivery method					
Normal vertex delivery	107 (82%)	20 (44%)	26 (53%)	28 (39%)	181 (61%)
Caesarean section	11 (8%)	23 (51%)	21 (43%)	39 (54%)	94 (32%)
Vaginal breech	12 (9%)	2 (4%)	1 (2%)	1 (1%)	16 (5%)
Forceps	0	0	0	4 (6%)	4 (1%)
Vacuum	0	0	1 (2%)	0	1 (0.3%)
Cause of death by PPIP category					
Immaturity	104 (80%)	24 (53)	4 (8%)	0	132 (45%)
Hypoxia	0	4 (9%)	13 (27%)	50 (69%)	67 (23%)
Infection	25 (19%)	15 (33%)	14 (29%)	7 (10%)	61 (21%)
Congenital anomaly	1 (1%)	2 (4%)	17 (35%)	10 (14%)	30 (10%)
Other	0	0	1 (2%)	5 (7%)	6 (2%)
Age at death, days: median (IQR)	1 (0 – 4)	2 (1 – 6)	2 (1 – 5)	2 (1 – 3)	1 (1 – 4)
Neonatal death category					
Early NND	108 (83%)	35 (78%)	41 (84%)	66 (92%)	250 (84%)
Late NND	22 (17%)	10 (22%)	8 (16%)	6 (8%)	46 (17%)

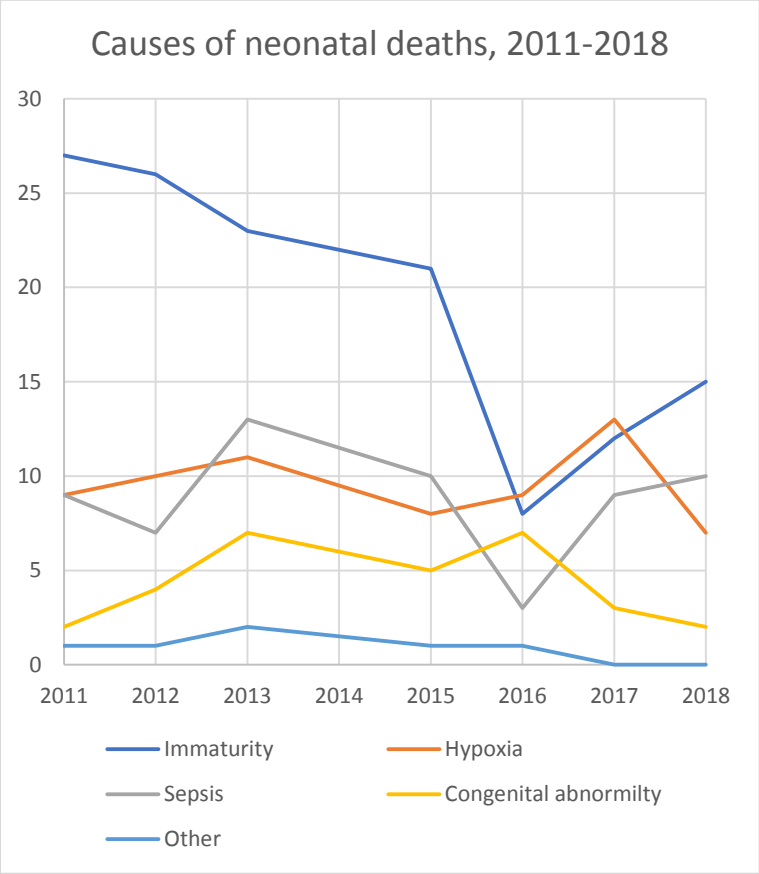
BBA: Born before arrival
MOU: Midwife obstetric unit
NSH: New Somerset Hospital
GSH: Groote Schuur Hospital
RCWMCH: Red Cross War Memorial Children's Hospital
PPIP: Perinatal Problem Identification Program
NND: Neonatal death

Table 2: Neonatal deaths per year of study

	2011 N=48	2012 N=48	2013 N=56	2015 N=45	2016 N=28	2017 N=37	2018 N=34
Rate of neonatal deaths, per 1000 admissions							
All	45.2	44.6	38.3	38.6	27.3	31.6	28.2
Inborn	44.9	47.1	34.6	41.2	30.6	29.2	22.5
Outborn	49.1	36.4	50.6	31.6	18.3	38.2	52.4
Causes of death by PPIP category							
Immaturity	27 (56%)	26 (54%)	23 (41%)	21 (47%)	8 (29%)	12 (32%)	15 (44%)
Hypoxia	9 (19%)	10 (21%)	11 (20%)	8 (18%)	9(32%)	13 (35%)	7 (21%)
Sepsis	9 (19%)	7 (15%)	13 (23%)	10 (22%)	3 (11%)	9 (24%)	10 (29%)
Congenital abnormality	2 (4%)	4 (8%)	7 (13%)	5 (11%)	7 (25%)	3 (8%)	2 (6%)
Sepsis	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (4%)	0	0
Birth weight categories of neonatal deaths							
Inborn:							
<1000g	25 (52%)	18 (38%)	12 (21%)	19 (42%)	5 (18%)	6 (16%)	12 (35%)
1000-1499g	2 (4%)	5 (10%)	8 (14%)	5 (11%)	1 (4%)	7 (19%)	3 (9%)
1500-2499g	4 (8%)	6 (13%)	6 (11%)	2 (4%)	7 (25%)	7 (19%)	4 (12%)
≥2500	5 (10%)	10 (21%)	13 (23%)	9 (20%)	10 (36%)	5 (14%)	3 (9%)
Outborn:							
<1000g	5 (10%)	5 (10%)	9 (16%)	2 (4%)	2 (7%)	3 (8%)	7 (21%)
1000-1499g	2 (4%)	1 (2%)	4 (7%)	1 (2%)	1 (4%)	3 (8%)	2 (6%)
1500-2499g	2 (4%)	3 (6%)	0	3 (7%)	0	4 (11%)	1 (3%)
≥2500	3 (6%)	0	4 (7%)	4 (9%)	2 (7%)	2 (5%)	2 (6%)
Age at death, days: median (IQR)	2 (1 – 4)	2 (1 – 4)	2.5 (1 -5)	1 (0 – 2)	1 (0 – 4)	1 (1 – 5)	1 (1 – 9)
Neonatal death category							
Early NND	41 (85%)	44 (92%)	46 (82%)	40 (89%)	25 (86%)	31 (84%)	24 (71%)
Late NND	7 (15%)	4 (8%)	10 (18%)	5 (11%)	4 (14%)	6 (16%)	10 (29%)
Specific causes of death							
HIE	3 (6%)	6 (13%)	6 (11%)	5 (11%)	6 (21%)	3 (8%)	3 (9%)
MAS/PPHN	5 (10%)	3 (6%)	4 (7%)	2 (4%)	3 (11%)	5 (13%)	3 (9%)
NEC	4 (8%)	3 (6%)	5 (9%)	4 (8%)	0	3 (8%)	0
Congenital syphilis	1 (2%)	1 (2%)	2 (4%)	0	0	0	0
Other sepsis	4 (8%)	3 (6%)	6 (11%)	6 (13%)	3 (11%)	6 (16%)	10 (29%)
HIV exposed	7 (15%)	9 (19%)	15 (27%)	14 (31%)	4 (14%)	15 (41%)	12 (35%)

PPIP: Perinatal Problem Identification Program
NND: Neonatal death
HIE: Hypoxic ischaemic encephalopathy
MAS: Meconium aspiration syndrome
PPHN: Persistent pulmonary hypertension of the newborn
NEC: Necrotising enterocolitis

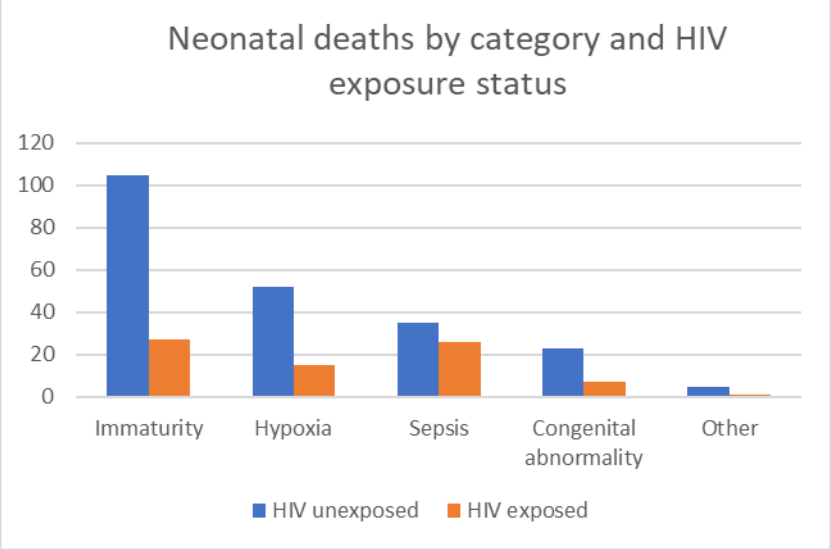
Figure 1: Causes of neonatal deaths, 2011-2018



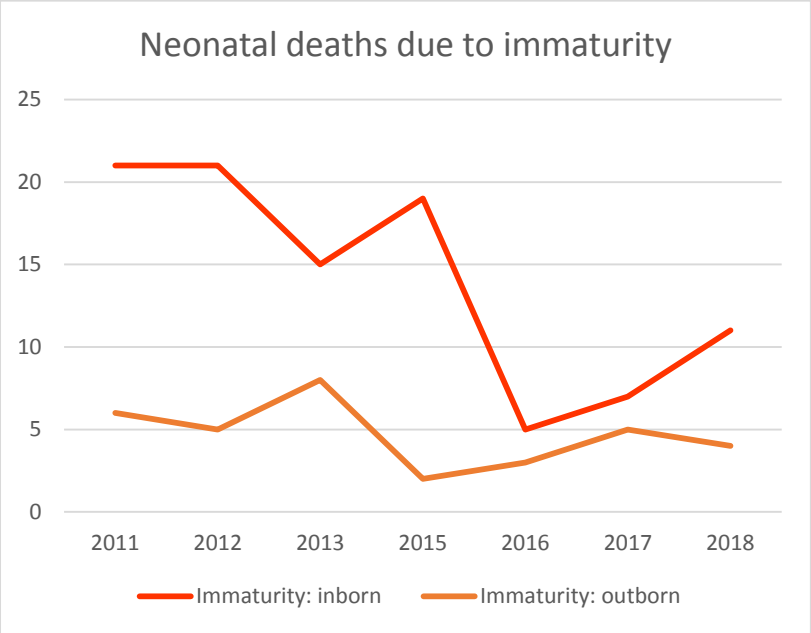
Supplementary table 1: Mean neonatal deaths per month, compared to recorded neonatal deaths in 2014, to illustrate incomplete data for several months

Month	Mean number of deaths per month, 2011-2013 and 2015-2018	Neonatal death, per month, in 2014
January	4.3	2
February	2.7	1
March	4.4	3
April	3.3	0
May	5.9	3
June	2.4	2
July	3.9	0
August	2.6	3
September	2.9	1
October	3.3	2
November	2.3	0
December	4.1	4

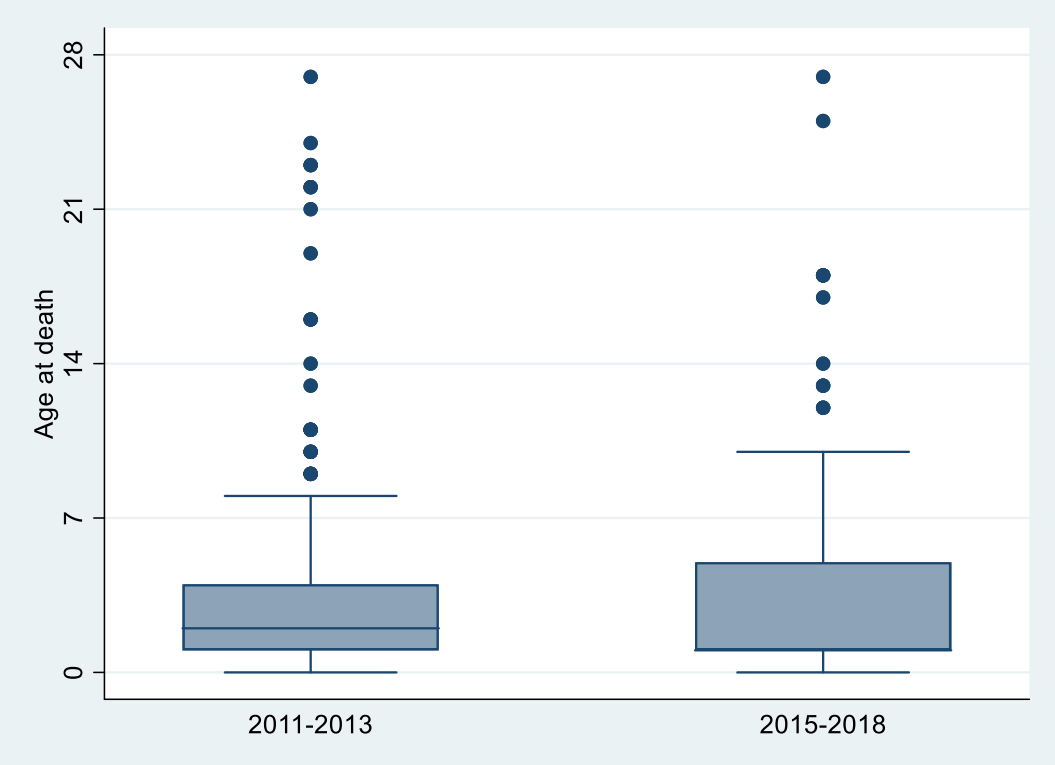
Supplementary figure 1: Causes of death of HIV-exposed and HIV unexposed neonates

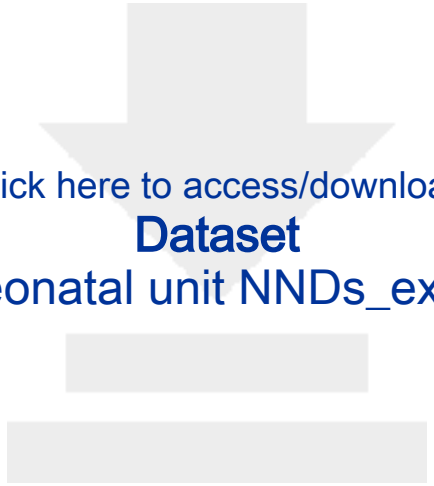


Supplementary fig 2: Decreases in numbers of neonatal deaths due to prematurity, by inborn status



Supplementary fig 3: Age at death, before and after implementation of high flow nasal cannula oxygen





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Dataset

9.1 Only neonatal unit NNDs_excl 2014.dta