OBSERVED BIRTH PREVALENCE OF STRUCTURAL CONGENITAL DISORDERS AMONG LIVE BIRTHS AT A REGIONAL FACILITY IN SOUTH AFRICA

By

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Submitted in partial fulfillment of the academic requirements

for the degree of MMed

in the Department of Paediatrics and Child Health

School of Clinical Medicine

College of Health Sciences

University of KwaZulu-Natal

Durban

2021

As the candidate's supervisor, I have approved this thesis for submission.

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Dedication

This thesis is dedicated to my parents.

Acknowledgements

All praise to Allah (SWT) for whose sustenance I was able to complete this thesis.

With sincere gratitude to:

- Dr Barnesh Dhada, the head of clinical unit in the Department of Paediatrics and Child Health at Greys Hospital, my supervisor for his ongoing advice, teaching, and support.
- Professor Colleen Aldous and Dr Helen Malherbe, my co-supervisors, for their input and guidance.
- To my colleagues at the Edendale Hospital Neonatal Unit, for their support and encouragement throughout this endeavour.
- To my wife, Saaleha and my daughter, Nusaybah for their continued love, support, and understanding.

Overview

Congenital disorders (CDs) are a global health issue and an important contributor to childhood mortality and morbidity. In South Africa (SA), the size and nature of the problem is unknown because reporting of CDs has been unreliable. Inaccurate assessment and under-reporting have led to an underestimate of the contribution of CDs to the burden of disease. As SA undergoes a positive epidemiological transition, the CD burden will be expected to increase.

This study aimed to fill the void in empiric CD data in the country. The objectives were to measure the birth prevalence of CDs of live births and describe the pattern of CDs at a regional hospital in KwaZulu Natal Province in 2018 using the Birth Defects Notification Tool (BDNT) developed by the National Department of Health. The collected data was then compared with existing published data in SA and country-specific modelled estimates.

A retrospective, observational, descriptive review of CDs diagnosed within the neonatal service at Edendale Hospital (EDH) was conducted in 2018. All in-house live births diagnosed with CDs were included in the study. Stillbirths and neonates with identified CDs born elsewhere and referred to EDH after birth were excluded from the study. Data were obtained from the birth registry, neonatal admission register, and the individual BDNT.

A total of 117 neonates were diagnosed and notified with a CD from the 7516 live births examined at EDH. The total birth prevalence for the study period was 15.57 per l000 live births, which equates to 1 in every 64 live births affected by a CD at EDH in 2018. The most affected systems were the musculoskeletal (31.6%) and circulatory systems (18.8%). Birth prevalence rates of key CDs were comparable to previously published SA data and are in line with current modelled estimates.

This study responds to the paucity of birth prevalence data on CDs in SA and serves as a starting point for comparison locally and with other national and international data. It offers additional evidence on the health burden represented by CDs in SA and the need to address the surveillance, care and prevention of these conditions as a healthcare priority.

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Abbreviations

AMA	Advanced Maternal Age
BDNT	Birth Defect Notification Tool
CD	Congenital Disorder
CHD	Congenital Heart Defects
Child PIP	Child Healthcare Problem Identification Programme
CP	Cleft Palate
CT	Computed tomography
DS	Down Syndrome
EDH	Edendale Hospital
EUROCAT	European Registration of Congenital Anomalies
FASD	Fetal Alcohol Spectrum Disorder
HIV/AIDs	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
ICD	International Classification of Disease
IMR	Infant Mortality Rate
KZN	KwaZulu-Natal
LMIC	Low and Middle Income Countries
MGDb	Modell Global Database of Congenital Disorders
MGEP	Medical Genetics Education Program
NCDs	Non-communicable Diseases
NCDSS	National Congenital Disorder Surveillance System
NDoH	National Department of Health
NTD	Neural Tube Defects
OFC	Orofacial Clefts
PCR	Polymerase Chain Reaction

PDA	Patent Ductus Arteriosus
SA	South Africa
TB	Tuberculosis
VACTERL	Vertebral-Anorectal-Cardiac-Tracheo-Esophageal-Renal-Limb
WHA	World Health Assembly
WHO	World Health Organisation

CHAPTER ONE: THE REVIEW OF LITERATURE

2.1 INTRODUCTION

Congenital Disorders (CDs) are a global health problem and an important contributor to childhood mortality and morbidity. Despite the 2010 World Health Organization's (WHO) World Health Assembly (WHA) Resolution WHA63.17[(1)] to recognize and prioritize CDs as a public healthcare issue, global estimates for 2010-2014 indicated that approximately 5 million births were affected by serious CDs, 2.5 million children under the age of five demised from CDs, and a further 2 million children surviving at the age of 5 years developed significant disability[(2)]. This lack of prioritization is particularly evident in developing nations, including South Africa (SA), where the CD burden is largely underestimated.

This literature review aims to highlight the issue of CDs as a public healthcare concern in SA. It begins with the definitions and terminology of CDs followed by a review of the epidemiological transition. The birth prevalence rate and mortality of CDs are then discussed and it concludes with an overview of CDs in SA.

2.2 DEFINITIONS AND TERMINOLOGY

CDs are defined as any potential pathological condition arising before birth, including disorders caused by environmental, genetic, and unknown factors, whether they are evident at birth or become manifest later in life[(3)]. Comparably, birth defects are defined as abnormalities of structure or function, including disorders of metabolism, which are present from birth. These may be clinically obvious at birth or may be diagnosed later in life. This includes CDs with genetic, partially genetic, teratogenic and unknown causes[(3, 4)]. Following

the global lack of agreement on terminology related to CDs, an international consensus was reached in 2006 by the WHO to use the terms 'CDs' and 'birth defects' synonymously[3].

Despite this international agreement on terminology, the continued use of disparate terms, which include congenital defects, congenital anomalies and congenital malformations, has resulted in significant variation in CD reporting and surveillance[5].

2.3 EPIDEMIOLOGICAL TRANSITION

The epidemiological transition described by Omran[6] occurs when there is a change in population health statistics and pattern of disease in a country or region, resulting from changes in socio-economic, educational, infrastructural and healthcare development[4, 7]. According to Omran's model, as mortality rates decline and life expectancy increases, countries transition through three stages of diseases[6]. In stage one, with epidemics, famine and war as the main cause of death, mortality is high and life expectancy at birth is low. In stage two, mortality starts to decline accompanied by an increase in life expectancy at birth. However, the levels of communicable diseases remain high. With improved control of communicable diseases, reduction in malnutrition and improved general healthcare, countries enter the third stage of the transition. In this stage, with improved life expectancy at birth and further reductions in mortality, non-communicable diseases (NCDs) and degenerative diseases emerge.

As developed countries entered the third stage of transition in the 1950s and 1960s [4] CDs began to surface as a public healthcare concern, resulting in the increasing need for medical genetic services to improve individual patient outcomes and overall population health[8]. As many developing nations are yet to transition into Omran's third stage, a relative increase in

the proportion of morbidity and mortality due to CDs will be expected and improved resource allocation to medical genetic services will be required for the care and prevention for those affected.

2.4 CD BIRTH PREVALENCE RATES

Prevalence is defined as the total number of existing cases in the population at a particular time[9]. Birth prevalence is the number of infants affected in one or a defined collective group of CDs per 1000 live births[4] and is the preferred measure to indicate the frequency of CDs[10]. Measuring the prevalence of CDs at birth is useful in establishing baseline rates, documenting changes over time and allows for comparison between populations to help ascertain possible aetiology and estimate the human and financial burden on the country's health, education and social support facilities.

The birth prevalence of CDs is variable from country to country and ranges from less than 10 to up to 80 per 1000 live births [11-16]. This considerable variation may be attributed to the complex interaction of known or unknown genetic and environmental factors which include racial, social, cultural and ethnic variables[17] or may reflect differing methods, inadequate systems, and poor implementation of surveillance and documentation.

In developed countries, for example, the United Kingdom, CD registration and surveillance systems are utilised, to ensure accurate birth prevalence rates and information are available allowing for relevant decision-making and policy development for care and prevention. In developing countries, where approximately 90% of CDs occur[1, 4] these registries and surveillance systems are almost non-existent.

In Africa, birth prevalence data on CDs is limited. Previous studies in Sub-Saharan Africa have demonstrated CD birth prevalence rates of between 16 to 20 per 1000 live births in some countries[18, 19]. However, the unavailability of accurate CD data has resulted in an underestimation of the true impact of CDs on the disease burden on the African continent[7, 8, 20].

2.5 CDs AND CHILD MORTALITY

During the epidemiological transition, CD deaths remain hidden among deaths due to communicable diseases and only surface once these diseases are better controlled[7, 8]. As developed nations entered into the final stage of the transition in the early 1960s, CDs began to emerge as an important contributor to childhood mortality. In England and Wales, a comparative study undertaken by McKeown[21] for the years 1901 and 1971 revealed that despite significant reductions in NCDs, CD mortality remained unchanged. CDs continue to be the leading cause of death in infant and under-five mortality in developed nations, accounting for up to 28% of deaths[22].

In developing countries, where over 90% of CDs presently occur, approximately 95% of those CDs demise due to the lack of adequate services for their care and management[4]. In SA, a mortality audit using the Child Healthcare Problem Identification Programme (Child PIP) by Patrick et al[23] highlighted the magnitude and nature of the health challenge posed by CDs among deaths. The review of mortality data in Child PIP for the period of 2005 to 2017 indicated that for every 1000 children who died, four died as a direct result of a CD with the overall CD burden estimated at 3.2% of the 60 575 audited deaths.

As SA experiences a positive epidemiological transition with significant reductions in childhood mortality, the proportions of deaths resulting from CDs will be expected to increase.

2.6 CDs in SOUTH AFRICA

In South Africa (SA), before the Human Immunodeficiency Virus / Acquired Immune Deficiency (HIV/AIDS) pandemic, CDs were emerging as a healthcare need.

In the early 1990s, the South African Birth Defects Surveillance System (SABDSS), was established in Western Cape. This CD surveillance system aimed to provide information on the extent of disabling conditions in the community for the planning of a programme of prevention and rehabilitation[24, 25]. Data emanating from this surveillance system was submitted to the International Clearinghouse, a global birth defect monitoring system that was established in 1974[25]. In 1995, Delport et al[26] reported a CD birth prevalence of 11.87 per 1000 live births among black neonates in an urban hospital in Pretoria. With this figure being comparable to developed nations and with SA's reduction of childhood mortality in the early 1990s, it was anticipated that the country was entering the third stage of the epidemiological transition.

A national task force was convened and together with the WHO, the National Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities was published in 2001[27]. This policy document outlined the goals, objectives, strategies and delivery of clinical and laboratory services appropriate for the prevention and care of CDs in SA[7, 27]. It also introduced the Birth Defect Notification Tool (BDNT) which highlighted priority CDs such as cleft lip and palate, club foot, Down syndrome, fetal alcohol

syndrome and neural tube defects. The BDNT was revised in 2006 and is still employed today and forms part of the National Congenital Disorder Surveillance system (NCDSS). Further policy and education programmes targeting primary health care providers were developed[28] but the subsequent HIV/AIDS and Tuberculosis (TB) epidemics halted the growing momentum and commitment towards addressing and recognizing the CD burden of disease.

An audit of the NCDSS by Lebese et al[29] in 2014 identified major challenges with the current system. This included non-compliance of vital registration data, limited human and financial resources to manage the system and the lack of medical genetics services. This led to a significant underestimation of the CD burden in SA. With the shortage of accurate birth prevalence data, country-specific modelled data estimates indicate that up to 98% of CDs are under-reported in SA[29].

With significant reductions in childhood mortality rates mainly due to the successful anti-retroviral treatment program and prevention of mother to child transmission of HIV/AIDS, SA re-emerges into the third stage of the epidemiological transition. Therefore CDs are once again expected to emerge as a growing healthcare priority.

2.7 THE RESEARCH QUESTION

What is the birth prevalence rate and pattern of CDs among live births in the neonatal service at Edendale Hospital; a regional hospital in KwaZulu Natal (KZN), SA?

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CHAPTER TWO: A SUBMISSION READY MANUSCRIPT

Title:

Observed birth prevalence of structural congenital disorders among live births at a regional facility in South Africa

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ABSTRACT

Title: Observed birth prevalence of structural congenital disorders among live births at a regional facility in South Africa

Keywords: birth defects, congenital disorders, congenital anomalies, birth prevalence, Edendale Hospital, South Africa

Background: Congenital disorders (CDs) are an important contributor to disease burden in developing countries, including South Africa (SA). The size and extent of the problem in SA is underestimated due to the lack of recent reliable data.

Objectives: To measure the birth prevalence of CDs among live births, and describe the pattern of CDs at Edendale Hospital (EDH) in KwaZulu Natal. The collected data will be compared with existing published SA data and modelled estimates.

Methods: A retrospective, observational, descriptive review of CDs diagnosed at birth within the neonatal service at EDH in 2018 was conducted. All in-house live births diagnosed with CDs were included in the study. Data were extracted from the birth registry, neonatal admission register and the individual Birth Defect Notification Tool (BDNT).

Results: There were 117 neonates diagnosed and notified with a CD from the 7516 live births examined at EDH. The birth prevalence was 15.57 per 1000 live births. The most affected systems were the musculoskeletal (31.6%) and circulatory systems (18.8%). Birth prevalence rates of key CDs were comparable to previously published SA data and are in line with current modelled estimates.

Conclusion: This study responds to the paucity of birth prevalence data on CDs in SA and serves as a starting point for comparison locally and with other national and international data. It offers evidence on the size and nature of the health burden represented by CDs in SA and the need to prioritize the surveillance, care and prevention of these conditions as a healthcare priority.

Introduction

Congenital disorders (CDs) are defined as structural or functional abnormalities of prenatal origin which are present at birth[1]. While the majority of CDs are due to genetic or partially genetic causes occurring pre-conception, a proportion occurs after conception due to abnormalities of the foetal environment, while the cause of many remain unknown[2]. As a group of conditions, CDs are a major contributor to the global burden of disease, with an estimated 5 million births affected by serious CDs[1], and global estimates for 2010-2014 indicating over 400 000 foetal deaths, 2.5 million under-five deaths and a further 2 million surviving at 5 years of age with significant disability[3]. In 2010, the World Health Assembly (WHA) reaffirmed the importance of CDs as a healthcare issue through the adoption of Resolution WHA63.17 and outlined actions for their management and prevention, and these remain relevant for the era of the Sustainable Development Goals and achieving some of the Goal 3 targets of decreasing neonatal and infant mortality rates by 2030[4,5]. Many of these actions are yet to be implemented by member states, including South Africa (SA).

While CDs affect all populations worldwide and represent a significant burden of disease, the scale of the burden varies between populations. True differences in these rates are due to maternal age distribution for chromosomal disorders, consanguinity practices affecting the rate of recessive, single-gene disorders and localised environmental factors (teratogens) impacting the rates of certain CDs[6]. The birth prevalence of most congenital anomalies remains similar between populations, with notable exceptions including isolated neural tube defects with a lower birth prevalence in Sub-Saharan Africa [6-8]. Greatest mortality and morbidity resulting from CDs is seen in low and middle-income countries (LMIC), with apparent differences in CD birth prevalence rates between these resource-limited countries

[1] CDs resulting in death or disability in the absence of care.

attributed to diverse diagnostic, care and prevention capabilities resulting in underreporting to varying degrees [9].

Quantifying the CD burden of disease has been underway for decades in many high-income countries resulting in empiric datasets collected through established surveillance systems, such as the European Registration of Congenital Anomalies (EUROCAT)[10]. Analyses of these data enable healthcare policy makers to develop and implement evidence-based, appropriate medical genetic services in response, for the care and prevention of those affected by CDs. However, in LMIC, empiric CD data is inadequate, unreliable or missing. While modelled data serves as a valuable tool in the interim, the long term collection of empiric CD data is required through relevant training to enable accurate and timely diagnoses and the development of appropriate surveillance systems[3]. In SA, evaluation of the full burden of disease represented by CDs is lacking. While concerted actions were undertaken in the late 1990s and early 2000s to develop medical genetic services (including surveillance) as CDs began to emerge as an important cause of child mortality and morbidity, commitment to CDs waned with the rise of the HIV/AIDS epidemic as the competing health priority[11-13]. Data published in 2016 from the current birth defect surveillance system implemented by the National Department of Health (NDoH) since 2006 highlighted inconsistent and unreliable data with significant underreporting of CDs compared to modelled estimates[14]. With the successful management of HIV/AIDS with highly active antiretroviral therapy, SA is going through a positive epidemiological transition once again and CDs are re-emerging as a key cause of neonatal, infant and child deaths as infectious diseases are better managed [11, 15-17].

To fill the gap in empiric CD data in the country, this study aims to: 1) Measure the birth prevalence of CDs among live births, and 2) describe the pattern of CDs at a regional hospital in KwaZulu Natal Province in 2018 using the Birth Defects Notification Tool (BDNT) developed by NDoH. Collected data will be compared with existing published data in SA,

including both historic research studies and modelled estimates. The study also includes a quality improvement aspect to promote and maintain accurate data as part of routine clinical care.

Method

Design

This study was a retrospective, observational, descriptive review of CDs diagnosed within the neonatal service at Edendale Hospital (EDH) in KwaZulu-Natal (KZN) Province, SA. The study period was from 01 January 2018 to 31 December 2018.

Study Setting

EDH is a regional (secondary level) healthcare facility located in the uMgungundlovu District in the city of Pietermaritzburg. It serves a predominantly urban population of around 1.4 million indigenous Zulu-speaking African people. EDH has well-organized obstetric services and a specialized Neonatal Care Unit, providing care for in-house cases and referrals from the surrounding state-run primary healthcare clinics, which provide obstetric and newborn care for uncomplicated deliveries. EDH provides care for an average of 600 in-facility deliveries a month, including normal and assisted deliveries, as well as those requiring neonatal intensive care facilities. This arrangement of a single, centralized neonatal care facility providing healthcare services to a relatively unchanging population provided a good setting to meet the objectives of this study.

Study Participants

As part of routine care, all in-house live births at EDH underwent a first neonatal examination within 24 hours of birth. Those identified with CDs were offered appropriate care as indicated and the BDNT was completed. These clinical records were included in the scope of this study, regardless of the gestational age of the baby. Stillbirths and other pregnancy losses

(spontaneous/induced abortions, including termination of pregnancy (TOP) due to foetal abnormality) were excluded as little routine clinical data is collected for these cases. Neonates with identified CDs born elsewhere and referred to EDH after birth were also excluded from the study to avoid inflating the birth prevalence rate as the number of deliveries at referral sites was not accessible within the study.

Case Definition

For the purposes of this study, *congenital anomalies* only (a sub-set of CDs) were recorded. These were defined as a physical or anatomical abnormality detected at birth (before discharge) and classified according to categories listed in Chapter XVII: Congenital Malformations, Deformations, and Chromosomal Abnormalities (Q00-Q99) of the International Classifications of Diseases (ICD10), 1997[18]. Based on this case definition, functional CDs and other CDs listed elsewhere in the ICD-10 system that are not easily recognisable and therefore not identified during the admission were not included in the study.

Congenital anomalies included in the study scope were categorised into major and minor conditions. Major or serious anomalies are those that may result in death, limited life expectancy or lifelong disability, particularly in the absence of care[9], whereas minor anomalies have little impact on health status or quality of life[9, 19].

Case Ascertainment and Data Collection

Details of all deliveries at EDH are recorded in the birth registry maintained by the Obstetric Unit team. All live-born neonates are examined within 24 hours of delivery prior to discharge by a midwife or a doctor in the Neonatal Unit team as a part of current clinical care. At the time of the study, the medical team comprised full-time neonatologists and general paediatricians, with the daily care team also including rotating paediatric registrars, medical officers (3 monthly) and interns (monthly). Following this assessment, healthy neonates and

those diagnosed with minor CDs and not requiring further care remained with their mothers in the post-natal units and were routinely discharged within 48 hours of delivery (longer for weekend deliveries). Neonates and mothers with no complications may be discharged as early as six hours post-delivery. Sick neonates and those with serious CDs were admitted to the Neonatal Unit to ascertain the extent of the abnormality and to undertake appropriate diagnostic testing. These admissions were recorded in a neonatal admissions register maintained by the Neonatal Unit team. Holistic management of neonates with CDs included genetic counselling offered to the parents and notification of the CD using the BDNT as part of routine clinical care by the neonatal medical team. For complex cases, the team had access to a general Paediatrician with a special interest in clinical genetics for assistance with diagnosis, care and/or genetic counselling. A gatekeeping system for genetic testing ensured referral and/or consultation to relevant genetic specialists at a tertiary hospital was implemented to ensure appropriate tests are requested.

Data for this retrospective study was extracted from the birth registry, neonatal admission register and the individual BDNT forms (all paper-based). Incomplete BDNT forms or more complex cases requiring a dysmorphology evaluation and syndrome identification (e.g. multiple anomalies) required the researcher to review individual clinical records and update the BDNT forms. All original BDNT forms were kept on file within the Neonatal Unit. As reported by Lebese et al, and during feasibility assessment for the study it was important to ensure that the BDNT was accurately and fully completed for all identified cases with CDs to enhance data quality. To achieve this, the researcher/first author clinically rotated through the neonatal unit for 3 months during the study period and served as a local champion for the span of the project to strengthen active surveillance by raising awareness of CDs, the BDNT surveillance process and reminding staff to complete the tool and to review the completeness of the forms on a monthly basis. Completed BDNT forms were submitted to the hospital

coordinator every month for onward submission through routine channels in the district health system as required by the NDoH. The functionality of this system outside EDH was beyond the scope of this study.

Data Analysis

The in-facility live birth prevalence rate was calculated using the number of live births with congenital anomalies as the numerator and the total number of live births at EDH as the denominator, reported as a rate per 1 000 live births. The birth prevalence rates of major, minor (i.e. polydactyly) and isolated CDs in diagnostic sub-categories were reported separately. To prevent double-counting, neonates with syndromes and multiple anomalies were counted only once in the overall live birth prevalence in the relevant sub-category and not for each specific anomaly. For example, a neonate with Trisomy 21 with a ventricular septal defect and trachea-oesophageal fistula was counted under Down syndrome only and not separately under circulatory and digestive systems.

Ethics

Ethical clearance was granted for this study by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Ref No. BE409/18). Gatekeeper permission to conduct the study was obtained from the Chief Executive Officer at EDH and the study was registered on the National Health Research Database. All data were collected retrospectively from routine care records or registers and were anonymized at the point of collection with a sequential study number allocated to protect all patients' identities and personal records. The data collection tool used was an anonymized copy of the BDNT. There was no direct patient contact in this study therefore individual patient consent was not required for ethical clearance. Collected data was stored electronically on password-protected drives and computers.

Results

Over the 12-month study period, 117 neonates were diagnosed and notified with congenital anomalies from the 7 516 live births examined at EDH. The total (major and minor CDs) birth prevalence for this period was 15.57 per 1000 live births affected. This equates to 1 in every 64 live births affected by a congenital anomaly at EDH in 2018. Excluding polydactyly - a minor congenital anomaly - the birth prevalence decreased to 13.44 per 1 000 live births, equivalent to 1 in 74 births.

The demographic characteristics of the affected births are outlined in Table 1. Congenital anomalies were more prevalent in male, term neonates with birth weights greater than 2500g. Advanced maternal age (AMA), defined as age greater than and equal to 35 years taken from the Obstetric Births Register accounted for 13% of all pregnancies. Of the 117 affected births, 20 (17%) were indicated as mothers of AMA on the BDNT however for 29 (25%) cases the AMA was not recorded.

Reported congenital anomalies categorised according to ICD-10 classification are detailed in Table 2. Anomalies of the musculoskeletal system were most frequently observed, accounting for just under a third (31.6%) of total anomalies recorded in the study period. Excluding polydactyly reduced the proportion of musculoskeletal anomalies to 18.9%, equivalent to the proportion recorded for the circulatory system (18.8%).

Polydactyly was the most common individual condition observed, accounting for 13.7% of total congenital anomalies identified. The other most frequently reported conditions were Down syndrome (DS, 11.1%), Congenital Talipes Equinovarus (9.4%) and Neural Tube

Defects (NTDs, 4.3%) which are all regarded as priority conditions[2] by the NDoH[20]. Equal numbers of isolated Cleft Palate (CP) were reported as for isolated cleft lip/cleft lip and palate (collectively 4.3%).

Other than chromosomal disorders, the aetiology of most congenital anomalies observed in this study were malformations due to multifactorial or unknown reasons. Some were less visible, internal malformations, including several congenital heart defects (CHDs). Some single gene disorders (8%) with obvious phenotypes were also reported.

Eight (9.4%) of the affected neonates were diagnosed with multiple congenital anomalies. In some cases, these were recognisable syndromes due to teratogen exposure during pregnancy (Foetal warfarin syndrome and Foetal alcohol syndrome), known genetic mutations (Cornelia De Lange syndrome) or due to associated congenital malformations including Vertebral-Anorectal-Cardiac-Tracheo-Esophageal-Renal-Limb (VACTERL) association and Pentalogy of Cantrell, due to unknown causes.

The proportion of affected neonates that underwent investigations are summarised in Table 3. Of the 117 affected neonates identified, 96 (82%) underwent relevant blood and imaging investigations including hormonal testing, congenital infection screening, x-rays, ultrasound, echocardiography or computed tomography (CT) scans. Of all cases, 25 neonates underwent Trisomy polymerase chain reaction (PCR) blood testing, 15 (60%) were confirmed as Trisomy (13, 18 or 21). A further 9 were recorded as having karyotype testing with 7 normal results and for 2 the results were lost by the testing laboratory.

The birth prevalence rates of key congenital anomalies observed in this study were compared with rates obtained by other similar South African studies, presented graphically in Figure 1.

[2] List of priority conditions to be notified at birth compiled by NDoH in 2001[12]: DS, NTDs, albinism, microcephaly, OFC and isolated hydrocephalus. These were revised in 2004[13] to include congenital talipes equinovarus, congenital infections, congenital deafness, blindness, physical handicap and mental retardation[12, 14].

The highest birth prevalence rates were observed by Venter and Christianson et al[21] the only rural study - for three of the congenital anomalies profiled (Down syndrome, anencephaly and spina bifida). The highest overall birth prevalence was recorded for Congenital Talipes Equinovarus by Pompe van Meerdervoort et al[22] in the 1970s. Birth prevalence rates recorded in the present study were comparable for the majority of anomalies, but were lowest for spina bifida and highest for Orofacial Clefts (OFC).

In Table 4, live birth rates observed in the current study were compared to modelled national estimates for South Africa in 2017 generated via the Modell Global Database of Congenital Disorders (MGDb)[6, 23-26]. The MGDb method combines robust, observed data from well-established surveillance systems with demographic data to produce baseline (no interventions) and actual (current care) estimates, using the infant mortality rate (IMR) as a proxy to quantify available services[6, 23, 24]. For two of the conditions compared; namely Down syndrome and OFC, the observed birth prevalence in the current study was higher than MGDb estimates for South Africa. Observed and modelled birth prevalence rates for NTD were the same, and the observed birth prevalence rate for CHDs was less than the modelled estimate from MGDb for South Africa in 2017.

Table 1. Demographic characteristics of the study cohort

Category	Characteristic	Number	Proportion (%)
Gender	Male	60	51,3%
	Female	54	46,2%
	Ambiguous	3	2,6%
Population Group	African	116	99,1%
	Other	1	0,9%
Birth Weight	<2500g	51	43,6%
	>2500g	66	56,4%
Gestational Age	<37 weeks	48	41,0%
	>37 weeks	69	59,0%
Advanced Maternal Age	>35 years	20	17,0%
	<35 years	68	58,0%
	Not recorded	29	25,0%

Table 2. Number and birth prevalence of congenital anomalies diagnosed in live births at Edendale Hospital in 2018, categorised according to ICD-10 groupings. Minor CDs[3] and CDS designated as priority conditions in South Africa are indicated footnotes by symbols.

System/Syndrome	Classification	Aetiology	Number (n=117)	Percentage of CDs (%)	Birth Prev. per 1000 LB
Musculoskeletal			37	31,6%	4,92
	Postminimus Polydactyly*	Single Gene Disorder	16		2,13
	Congential Talipes Equinovarus†	Constraint/Multifactorial	11		1,46
	Gastroschisis	Multifactorial	3		0,40
	Achondroplasia	Single Gene Disorder	3		0,40
	Omphalocoele	Multifactorial	2		0,27
	Thanotophoric dysplasia	Single Gene Disorder	1		0,13
	Prune Belly Syndrome	Unknown	1		0,13
Circulatory System			22	18,8%	2,93
	Ventricular Septal Defect	Multifactorial	8		1,06
	Atrial Septal Defect	Multifactorial	5		0,67
	Atrioventricular Septal Defect	Multifactorial	3		0,40
	Patent Ductus Arteriosus	Multifactorial	3		0,40
	Tetralogy of Fallot	Multifactorial	2		0,27
	Pulmonary Stenosis	Multifactorial	1		0,13
Chromosomal			15	12,8%	2,00
	Down Syndrome (Trisomy 21)†	Chromosomal Abnormality	13		1,73
	Edwards Syndrome (Trisomy 18)	Chromosomal Abnormality	1		0,13
	Patau Syndrome (Trisomy 13)	Chromosomal Abnormality	1		0,13

[3] Other CDs may have a variable impact on health status or quality of life, depending on severity, e.g. PDA, VSD, ASD, Omphalocoele, facial dysmorphology, but for the purpose of this study most were categorised as major anomalies. Umbilical hernias were excluded.

* Minor congenital anomaly.

† Designated as a priority CD in South Africa [12].

Nervous System			9	7,7%	1,20
	Anencephaly†	Multifactorial	3		0,40
	Spina Bifida (Meningomyelocoele)†	Multifactorial	2		0,27
	Arnold Chiari Malformation – Hydrocephalus	Multifactorial	1		0,13
	Congenital Hydrocephalus†	Multifactorial	1		0,13
	Dandy Walker Syndrome	Multifactorial	2		0,27
Digestive System			7	6,0%	0,93
	Tracheo-oesphageal Fistula	Multifactorial	2		0,27
	Duodenal Atresia	Unknown	1		0,13
	Small Bowel Atresia (Jejunal)	Unknown	2		0,27
	Jejunal Atresia - Type 4	Unknown/Multifactorial	1		0,13
	Small Bowel Malrotation	Unknown	1		0,13
Orofacial Clefts (Isolated)			4	3,4%	0,53
	Cleft Lip†	Multifactorial	2		0,27
	Cleft lip & palate†	Multifactorial	2		0,27
Eye, Ear, Face and Neck			3	2,6%	0,40
	Treacher Collins Syndrome	Single Gene Disorder	1		0,13
	Facial dysmorphism*	Unknown	2		0,27
Genital System			3	2,6%	0,40
	Ambiguous Genitalia (DSDs)	Multifactorial	2		0,27
	Hypospadias	Multifactorial/unknown	1		0,13
Respiratory System			3	2,6%	0,40
	Choanal Atresia	Unknown	2		0,27
	Congenital Cystic Lung	Unknown	1		0,13
Skin			3	2,6%	0,40
	Neurofibromatosis	Single Gene Disorder	1		0,13
	Epidermolysis bullosa	Single Gene Disorder	1		0,13
	Tuberous Sclerosis	Single Gene Disorder	1		0,13
Other Congenital Disorders & Multiple Malformations			11	9,4%	1,46

	VACTERL Association	Multifactorial	3		0,40
	Fetal Alcohol Syndrome	Teratogen	2		0,27
	Fetal Warfarin Syndrome	Teratogen	1		0,13
	Cornelia De Lange Syndrome	Single Gene Disorders	1		0,13
	Pentalogy of Cantrell	Unknown	1		0,13
	Ambiguous Genitalia & Imperforate Anus	Unknown	1		0,13
	Club feet & facial dysmorphism (Possible Trisomy)	Unknown	1		0,13
	Imperforate Anus + Club feet (Possible VACTERL)	Unknown	1		0,13
Total			**117**	**100,0%**	**15,57**

Table 3. Summary of investigations

Investigation	Number (n = 117)	Proportion (%)	Investigation
Relevant investigation	96	82%	Blood & Radiology
Chromosomal Analysis	25	21%	15 (60%)
Biochemical Analysis	0	0%	Not recorded on form
DNA/Molecular Analysis	0	0%	N/A in KZN at the time of study
Karyotype	9	8%	7 were normal, 2 lost by lab

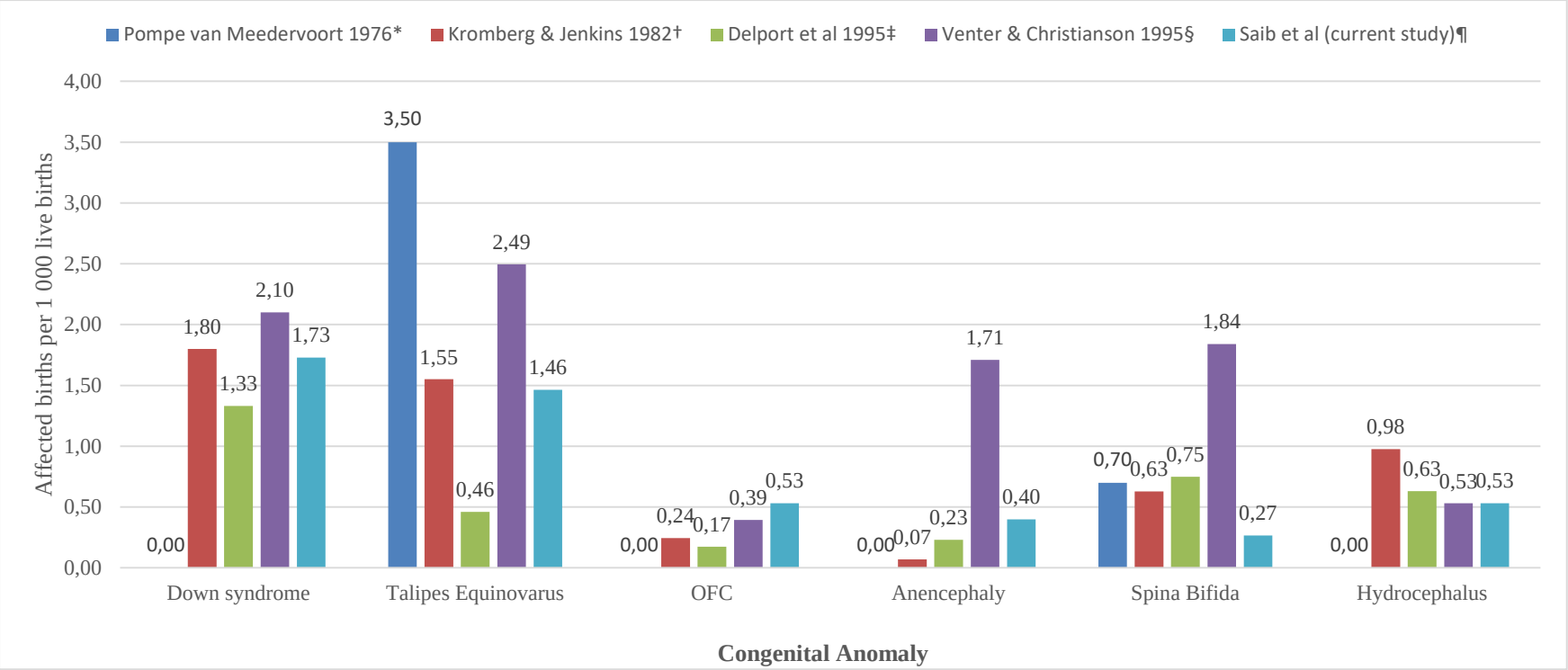

Figure 1. Comparison of birth prevalence rates for key congenital anomalies from the current study with rates observed by other hospital-based studies in South Africa

*Pompe van Meedervoort 1976: Prospective,75% urban hospital-based study (Pelonomi Hospital, Bloemfontein, Free State), 10 000 live births over 3 years[22]
†Kromberg & Jenkins 1982: Retrospective, urban hospital-based study (Chris Hani Baragwanath Hospital, Johannesburg, Gauteng), 28 689 live births over 2 years[27]
‡Delport et al 1995: Prospective, urban hospital-based study (Kalafong Hospital, Pretoria, Gauteng), 17 351 live births over 3 years[28]
§Venter & Christianson 1995: Prospective, rural, hospital-based (Mankweng Hospital, Limpopo), 7 617 live births over 3.5 years[21]
¶Saib et al 2020: Retrospective, predominantly urban, hospital-based (Edendale Hospital, Pietermaritzburg, KwaZulu Natal), 7 516 live births over one year (current study).

Table 4. Comparison of observed live birth prevalence of selected congenital anomalies with estimates generated by the Modell Global Database (MGDb) of Congenital Disorders[23].

	BIRTH PREVALENCE PER 1 000 LIVE BIRTHS		SAIB 2020 Comparison with MGDb-2017
	MGDb: 2017*	SAIB 2020 (Current Study)	
Down syndrome	1,52	1,73	114%
NTD	0,67	0,67	100%
OFC	0,22	0,53	241%
CHD	3,12	2,93	94%

*Actual live birth rates generated by MGDb 2017 with deductions for stillbirths/foetal death, termination of pregnancy, and affected births converted to healthy conceptions through pre-natal care including folate fortification[23].

Discussion

This study measured the birth prevalence of congenital anomalies among live births at EDH in KZN, South Africa from January to December 2018. Examination of all newborns and recording of all anomalies identified at birth (before discharge) were reported using the enhanced BDNT for notification to the NDoH. Data collected was described and compared with existing published data for congenital anomalies in SA, including historic research studies and modelled estimates.

Study Strengths

This was the first facility-based study conducted to determine the birth prevalence of congenital anomalies in KZN, with all previous similar published studies taking place in other provinces.

Facility-based studies such as this include all (live) births occurring at the participating centre. For this study, the total number of births undertaken at EDH was confirmed via the birth registry and other data were collected from the neonatal admission register and the patient-specific BDNT form. This facility-based study, incorporating active surveillance, is more feasible for large, diverse populations, particularly in LMICs such as SA where health care resources (both human and financial) are severely constrained. While this type of studies may be subject to referral bias due to births by non-residents and referrals from outlying clinics, it offers the advantage of obtaining high-quality data on key conditions at sentinel sites. The alternative, population-based study approach is unaffected by this type of bias as the population is not selected and includes all (home and facility-based) deliveries. However, population-based studies are more suited for smaller populations or regions or by sub-

national systems due to the higher cost and infrastructure required, as has been demonstrated by poor data resulting from the population-based BDNT implemented in SA[29].

The collection of accurate data is essential for precise CD surveillance. Prior to the study, a passive surveillance approach yielded approximately 3 to 6 CDs per 600 deliveries on average per month at the study facility (Personal communication Dr Bhoola, Head of Clinical Unit 2017). In this study, an active surveillance approach supported by a clinical champion resulted in 10 CDs per 600 deliveries on average per month. This simple and effective strategy improved CD detection and offers a feasible methodology for sites with similar resources in other LMIC contexts.

Study Challenges

Before a congenital anomaly can be reported it must first be accurately and timeously diagnosed. This requires appropriately trained healthcare professionals (HCPs) able to accurately diagnose congenital anomalies and compliance with reporting requirements of a surveillance system as a part of routine clinical care. Genetics content included in both medical school and nursing college curricula is lacking[30-32], and varies greatly between institutions and countries, resulting in many HCPs lacking relevant genetics knowledge, skills and expertise. In SA, specialised medical genetic services are inadequate, with only 12 practising clinical medical geneticists and an equivalent number of genetic counsellors countrywide, equivalent to 1 per 5 million of the population rather than the recommended 1 per million for clinical medical geneticists and 1 per 580 000 for genetic counsellors[33, 34]. KZN lacked a clinical medical geneticist for decades until a post was established in late 2018 following intense advocacy efforts, making one such specialist available to the 11m population of the province. Recruitment of a genetic counsellor is underway and centralised

provincial genetic services are developing out of the tertiary hospital in Durban with the support of two genetic nurses. Despite historic shortfalls in genetic services, KZN was reported by Lebese et al in 2014 as the province with the greatest reporting compliance contributing over 50% of national surveillance data, even following the loss of an effective provincial coordinator in 2012 [14]. In this study, complex cases were referred to a paediatrician with a genetics interest in lieu of a medical geneticist. This individual has received training in the Medical Genetics Education Program (MGEP) and five years of experience running a specialist level referral clinical genetics clinic at the nearby tertiary hospital in Pietermaritzburg. The team neonatologists have had no formal genetics training other than their sub-specialty training which included access to a feto-maternal anomaly clinic at the training site. The remainder of the medical team lack specialist genetics training. Team midwifery skills and expertise were not explored in this study. These on-going deficits highlight the urgent need for capacity building at all levels, together with appropriate accompanying resources to improve the surveillance, care and prevention for those affected by CDs. While the gatekeeping system involving the referral of patients to genetic specialists at tertiary hospitals ensures appropriate tests are requested, this places an additional stress on a poorly resourced system.

The ongoing use of paper-based systems, including the BDNT, continues to impact surveillance compliance and quality of data reported, even when integrated as part of routine clinical care. Within this study, active surveillance rather than the routine passive approach was implemented, combined with the champion-led initiative to improve quantity and quality of reporting. Quantification of this improvement through the review and comparison of BDNT forms before and during the study (effectively doubling the number of CD cases notified) highlights the impact of the champion-led initiative. However, to sustainably improve compliance and reporting quality a long-term solution is needed, preferably

incorporating notification of CDs as part of a centralised electronic patient record with mandatory ICD10 coding. By default, this would fill data gaps experienced in this and other similar studies, such as the number of mothers of advanced maternal age since the maternal date of birth were excluded on the BDNT – which would be accessible on a centralised system.

Several blood samples of the study cohort were lost by the testing laboratory. Anecdotal evidence suggests this is a common challenge in the province and largely systemic, with loss and leakage of samples occurring during transport from satellite to main laboratory sites. The additional cost implications and patient trauma due to repeated testing highlight the need for these challenges to be addressed.

Comparison with other data

Previous Studies

All the research studies used for comparison in this study were also facility-based studies, focusing on black South Africans, and two were prospective studies with the exception of the current study and Kromberg and Jenkins in 1982 (Table 4)[27]. The high variation in birth prevalence of NTDS between the studies may be attributed to the introduction of mandatory folate fortification of staple crops in 2003[35, 36]. Similarly, higher NTD rates reported by Kromberg and Jenkins (1982)[27] may be indicative of improved reporting via a retrospective approach, compared to other prospective studies. The high rates of spina bifida and anencephaly reported in a rural setting by Venter and Christianson et al[21] in comparison to other urban-based studies pre-dating folate fortification are still not yet elucidated and may be attributed to the complex interaction of genetic and environmental factors[44, 45]. The extremely high birth prevalence reported by Pompe van Meedervoort[22] for Congenital

Talipes Equinovarus may be due to the inclusion of both isolated and syndromic club foot whereas the current study differentiates between these aetiologies.

Based on previously reported birth prevalence rates by similar studies for oculocutaneous albinism - one of the most common single-gene disorders in SA - at least 2 affected births would have been expected in this study[21, 27, 28]. This absence cannot be explained.

Differences in birth prevalence rates of DS and other Trisomies may reflect differences in the proportions of mothers of AMA in the different studies, as well as challenges in identifying neonates with these conditions[37, 38]. Due to incomplete data on AMA in the current and previous studies, further analysis was not possible.

Comparison with modelled data

For three of the four conditions compared, MGDb modelled rates are either the same or less than those observed in this study (Table 4). The difference in observed and modelled rates for DS may be due to a difference in the proportion of mothers of AMA in the study cohort (17.0% versus 11.6% in MGDb[23]). The higher rates for OFC observed compared to both MGDb and previous study rates (Fig. 1) indicate increased ascertainment of isolated CP. In established registries elsewhere in the world with high rates of CP ascertainment, isolated CP accounts for 30-50% of total OFC which confirms the result of the ratio reported in this study[39]. The lower study rates observed for CHDs in comparison to modelled estimates may be due to invisible, undiagnosed CHD cases at birth, CHD cases diagnosed outside the study period, variation in case definitions, or indicate a need to refine the MGDb modelling approach for CHDs. Only significant Patent Ductus Arteriosus (PDAs) requiring surgical intervention were included in this study, accounting for the low number of PDAs relative to the number of premature births. The overall similarity of the study results with modelled

estimates serves to validate the MGDb approach for this condition, which may be of particular use in provinces where no similar studies have been undertaken.

Global comparison

Both the total birth prevalence (15.57 per 1 000 live births) and the birth prevalence excluding polydactyly (13.44 per 1 000 live births) are less than half the average birth prevalence of *congenital anomalies* (20-25 per 1 000 live births)[40-42]. These results are also far below the average birth prevalence of 37 per 1 000 live births for CDs in totality[40, 42].

Limitations

This study was limited to recording live births affected by congenital anomalies at EDH, and excluded affected stillbirths occurring in EDH and affected births (live births and stillbirths) occurring outside EDH, from both public and private facilities. The proportion of 'missed' CDs in stillbirths and early pregnancy losses remains an uncounted and unquantified element of the CD burden of disease in this setting.

The focus of the study on congenital anomalies only – a sub-set of CDs which excludes 40% of CDs included elsewhere in the ICD-10 system (e.g. inborn errors of metabolism) - prevents the quantification of the *total* CD-related burden of disease[17, 23]. Congenital infection data were also not actively collected in this study.

A further limitation of focusing on obvious congenital anomalies is that disorders less obvious at birth may not have been identified at birth or during initial neonatal admission and may have been excluded from the study findings. With an estimated 26% of CDs identifiable

at birth only, a significant portion of less obvious congenital anomalies in ICD-10 Chapter XVII[18] may not have been diagnosed before discharge [21, 43]. For example, Fetal Alcohol Spectrum Disorder (FASD) is challenging to diagnose at birth, with the majority of cases being picked up in school-age children.

Conclusion

This study is the first of its kind published from KZN and achieved the aim of quantifying the birth prevalence of live births affected by congenital anomalies at EDH in 2018, demonstrating the ability of this facility to collect high quality, accurate data on these conditions. It responds to the paucity of available birth prevalence data on congenital anomalies in SA. It also offers reassurance that this can be replicated in similar contexts and serves as a starting point for comparison of trends locally and with other national and international data. The observed study rates are in line with modelled estimates, indicating the further application of MGDb and other modelling approaches in under-served areas that lack resources to measure accurate data.

This study offers additional evidence on the health burden represented by CDs in SA and the need to prioritise these conditions, and their surveillance, care and prevention, as a healthcare priority. In order to respond appropriately to the growing health burden of CDs as infectious diseases are better controlled in SA, further studies of this nature are required to offer policy-makers reliable evidence for informed data-based decision making around essential health services and value-based allocation of available limited funding. This should be undertaken in tandem with improved, electronic surveillance systems if SA is to respond appropriately to specific local, regional and national health needs to prevent people with CDs from being left behind.

Further research is recommended on:

1) Increased scope of study to include:
    - Follow up prevalence studies incorporating other life-course stages including neonates, infants and children affected by CDs outside the birth period to identify all CDs (and quantify the total burden of disease) during these timespans.
    - Functional CDs included elsewhere in the ICD-10 system in addition to structural disorders included in the remit of this study.
    - Additional, similar studies undertaken in other regions of SA to enable comparison with this and previous studies to identify regional/demographic differences.
    - Similar studies on the birth prevalence of CDs in private healthcare settings.
    - Clinical care and outcomes measurement among CDs treated at hospitals currently, and how to improve this care from prevention through ante-natal identification and planning of services before birth to improve outcomes and quality of life.
2) Capacity building for HCPs on both clinical and genetic diagnosis of CDs and reporting strategies, including the BDNT, to promote improved diagnosis and more accurate, comprehensive reporting.
3) Investigate long-term options for improving CD reporting i.e. inclusion of CDs on the neonatal dashboard as a sentinel group of disorders to evaluate the return on investment enabled through diagnosis and care.

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Appendices

Appendix One: The Study Protocol

University of KwaZulu-Natal
College of Health Sciences
School of Clinical Medicine

Title: The Birth Prevalence Rate of Congenital Disorders among live births at a regional facility in South Africa.

Degree: Masters of Medicine – Paediatrics and Child Health (MMPCH)

Principal Investigator: Muhammad Zubayr Saib

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EXECUTIVE SUMMARY

STATEMENT OF PURPOSE

The purpose of this study is to determine the birth prevalence and pattern of congenital disorders (CDs) in neonates at a regional facility in South Africa (SA); namely, Edendale Hospital (EDH) in KwaZulu Natal (KZN) for the period 1 January 2018 to 31 December 2018. As a regional hospital in the SA district health system with a specialized neonatal care unit, EDH receives obstetric and neonatal referrals from the surrounding community and primary healthcare centres (CHCs and PHCs) in catchment area. This provides a good opportunity to measure a catchment population based birth prevalence and describe the pattern of CDs. The results of this study could allow comparison with modeled data and provide a better understanding of the actual needs for clinical and laboratory genetic services for the studied population. This could hold important lessons for healthcare planning and resource allocation in KZN, SA and other similar developing world contexts.

CDs are an important cause of childhood mortality and morbidity globally. The birth prevalence of CDs has shown variability within and between countries. CDs are an important measure of a healthcare systems progress against preventable causes of mortality as a country undergoes its epidemiological transition. Patterns of CDs may be useful in developing prevention strategies, exploring possible causes, assessing trends, changes and response to interventions for specific CDs over time.

In SA, there is a lack of accurate birth prevalence data for CDs. Attempts to improve this situation with a National Surveillance System using the Birth Defects Notification Tool (BDNT) have failed. This was confirmed at our study site when poor data collection forced a

change from retrospective to prospective design. All live born neonates identified with a CD will be recruited with data collection onto the current BDNT. Birth registers, clinical records and relevant laboratory records will be reviewed if the BDNT is poorly completed. This is to reduce missed cases and eliminate missing data to ensure an accurate birth prevalence measurement. The birth prevalence of CDs will be calculated per 1000 live births. Descriptive statistics will be used to describe the pattern seen in this study population.

Study results will be disseminated to the target audience by local presentation of findings at EDH, University of KwaZulu Natal (UKZN) research forums, submitted for publication in peer-reviewed SA medical journal and as a Master of Medicine thesis. The authors would like to contribute towards highlighting CDs as a growing current and future child healthcare need requiring appropriate resources in SA.

TABLE OF CONTENTS

1. BACKGROUND

1.1 INTRODUCTION

Congenital Disorders (CDs) or birth defects are structural and/or functional abnormalities of prenatal origin which are present at birth [(2)]. The birth prevalence of CDs is variable within and between countries. This variation may be attributed to a complex interaction of known or unknown genetic and environmental factors [(9)]. The prevalence rates can be useful in determining possible aetiology, assessing trends over time and developing care strategies and policies for future prevention.

CDs are a major contributor to childhood mortality and morbidity globally. Each year an estimated 7.9 million children are born with a serious birth defect, 3.3 million children under five years of age demise from birth defects, and 3.2 million children who survive may develop future disability (1).

In South Africa (SA), prior to the Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome (HIV/AIDS) pandemic, CDs began to emerge as a growing healthcare need. A study by Delport et al [(19)] in 1995, showed the incidence of CDs in black South African neonates in an urban setting to be 11.87 per 1000 live births or just over 1%. Since then National SA Policy Guidelines were established with a National CDs Surveillance system implemented in 2006. An audit of this surveillance system by Lebese et al [(20)] in 2015, indicated that up to 98% of CDs are under-reported in SA when compared to modeled data. Modeling indicated that a minimum of 6.8% of births in South Africa are affected by CDs [(13,21)]. The major challenges identified were the non-compliance of vital registration data, limited human and financial resources and the lack of medical genetic services in the country.

Furthermore, there is a lack of recent SA birth prevalence data for CDs. As SA undergoes its epidemiological transition with significant reductions in childhood mortality rates, CDs are expected to emerge as a growing healthcare need as has been in developed countries.

1.2 LITERATURE REVIEW

Congenital disorders (CDs), also known as birth defects, congenital malformations or congenital anomalies, are defined as abnormalities of structure or function, which include disorders of metabolism, that are present from birth [(2)]. CDs are a global health problem. Each year an estimated 7.9 million children are born with a serious birth defect, 3.3 million children under five years of age demise from birth defects, and 3.2 million children who survive may develop future disability [(1)]. Apart from the direct impact on affected children and families, CDs exert a huge financial burden on the country's health, education and social support facilities.

The birth prevalence of CDs is variable from country to country, and ranges from less than 1% to up to 8% [(3-8)]. This considerable variation may be attributed to the complex interaction of known or unknown genetic and environmental factors which include racial, social, cultural and ethnic variables or may reflect differing methods, inadequate systems, and poor implementation of surveillance and documentation [(9)]. In addition, incorrect decisions based on inaccurate data also contribute to wastage of limited resources, increased costs of care and ultimately poor outcomes for children with CDs.

In developed countries, CDs are a leading cause of neonatal and under five child mortality, accounting for up to 28% if deaths [(10)]. These countries, for example, the United Kingdom, employ registration and surveillance systems, which provide more accurate information allowing for decision-making and policy development relevant to prevention and care. In developing countries, where approximately 90% of CDs occur, these registries and surveillance systems are almost non-existent. The health services, from antenatal to adolescent healthcare, are challenged with fundamental gaps in the understanding, prevention, and treatment of these disorders [(11)]. This lack of prioritization of CDs in developing countries is concerning, and was acknowledged by the World Health Organsiation's (WHO) World Health Assembly (WHA) in 2010 with the passing of resolution WHA63.17, which aims to highlight CDs as a public health issue [(12)].

In Africa, the true impact of CDs on childhood morbidity and mortality is largely unknown. As most of middle to low income countries in Africa experience an epidemiological transition, with reduction in communicable diseases and malnutrition and a declining infant

mortality rate, a relative increase in proportion of morbidity and mortality due to CDs will be expected based on the experience of industrialized nations [13]. There are numerous studies from developed nations on the birth prevalence and patterns of CDs from well-designed large multicenter surveillance programmes [14-17]. However, data on CDs from population based studies in Africa are limited.

In a study from Lebanon, Franicine et al [18] assessed the incidence and type of major CDs over a 9 month period in 2 Lebanese hospitals. The authors report a prevalence rate of CDs of 2.4% with increased frequency of cardiovascular defects noted. In Uganda, Ndibazza et al [11], record a birth prevalence rate of major CDs of 20.3% from the Entebbe region in Uganda. In Nigeria, a similar prevalence study conducted in the Niger Delta by Abbey et al [22], determined a birth prevalence of CDs of 20.7%.

In South Africa (SA), prior to the Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome (HIV/AIDS) pandemic, CDs were emerging as a healthcare need. A study by Delport et al [19] in 1995, showed the birth prevalence of CDs in black SA neonates in an urban setting was 11.87 per 1000 live births. This figure is comparable to that of developed nations, however this study was limited in that it was not representative of the population of SA. Since then SA National Policy Guidelines were established and a National Congenital Disorder Surveillance system (NCDSS) was implemented in 2006. An audit of this surveillance system by Lebese et al [20]) in 2015 indicated that up to 98% of CDs are under-reported in SA when compared to modeled data estimates. The major challenges identified were the non-compliance of vital registration data, limited human and financial resources and the lack of medical genetic services in the country.

Furthermore, there is a lack of recent birth prevalence data for CDs in SA. As SA undergoes it's epidemiological transition with significant reductions in childhood mortality rates mainly due to the anti-retroviral treatment program and the prevention of mother to child transmission of HIV/AIDS, CDs are expected to again emerge as a growing healthcare priority.

1.3 THE RESEARCH QUESTION

What is the birth prevalence rate and pattern of congenital disorders (CDs) among live births in the neonatal service at Edendale Hospital; a regional hospital in KwaZulu Natal (KZN), SA?

2. AIMS AND OBJECTIVES

AIM

The aim of the study is to measure the birth prevalence rate and describe the pattern of congenital disorders (CDs) in live births in the neonatal service at Edendale Hospital; a regional hospital in KZN, SA.

OBJECTIVES

The objectives of the study are to:

- Measure the birth prevalence rate of CDs among live births.
- Describe the pattern of CDs in this study site.
- Describe the process of quality improvement (QI) of the surveillance and documentation system for CDs at the study site.

3. METHODS

3.1 Study Design

A prospective observational hospital based descriptive review of congenital disorders in the neonatal service at Edendale Hospital, KwaZulu-Natal, SA.

3.2 Setting

The study will be conducted in the neonatal service at Edendale Hospital.
Edendale is a town located in the Umgungundlovu district of KZN province of SA. It has a total population of 300 000 (2011 census), the majority being indigenous Zulu-speaking African descent. The well-organized state run healthcare infrastructure, consists of 24-hour community and 8-hour primary healthcare centres (CHCs & PHCs) which serve as first-contact entry points for obstetric and neonatal care. Next level care is referral to Edendale Hospital (EDH), the single regional healthcare institution with a specialized neonatal care unit in this catchment area. As there are no district hospitals, first level care also occurs here. EDH provides care for approximately 600 deliveries a month, with access to normal and assisted deliveries as well as neonatal intensive care facilities.

This arrangement of healthcare with a single centralized neonatal care facility provides a good opportunity to measure the birth prevalence and describe the pattern of CDs closer to population level, instead of modeled data.

3.3 Participant selection and Data Sourcing

The study will include all live births identified with congenital disorders (CDs) in the neonatal ward at EDH during the period of 01 January to 31 December 2018.

Stillbirths, spontaneous and induced abortions will be excluded as little routine data is collected on these cases in the hospital. Babies that are not born at EDH will also be excluded as births at other facilities will not be counted in the birth prevalence rate calculation. These limitations are important to overcome in future studies to get a proper population based measurement of the CDs.

Details of all deliveries at EDH are recorded in the birth registry maintained by the Obstetric Unit team. All live newborns are examined by a midwife, medical intern, paediatric medical officer or paediatric registrar within 24 hours of delivery. Normal neonates are usually discharged within 48 hours with follow-up at PHCs and CHCs. All admissions are recorded in the neonatal admissions register maintained by the Neonatal Unit team. The neonatologist in-charge or a Paediatrican conduct ward rounds daily, including on weekends and public holidays. One of the paediatrician's on staff has a special interest in clinical Paediatric Genetics.

The Birth Defects Notification Tool (BDNT), which forms part of the SA NCDSS will be the main data source. The BDNT is a paper-based tool completed by doctors once CDs are identified. These notifications are reported monthly to the KZN Department of Health (DoH).

Newborns with CDs are routinely admitted, extent of abnormalities ascertained, appropriate diagnostic testing done, holistic management with counseling performed and notified using the BDNT. If this process is incomplete or data is missing, clinical and laboratory records will be reviewed to ensure that the study aim can be achieved. Clinical staff will be encouraged and supported to complete the BDNT as thoroughly as possible to minimize the need to review other records and to save time during data collection. This process will be reported as a quality improvement (QI) activity.

3.4 Measurements

All data will be extracted from recorded clinical care and surveillance tools. No direct patient measurements will be carried out by the researcher/s.

3.5 Data Collection and Analysis

Data will be collected primarily from the births register, neonatal admissions register, BDNT, and the clinical and laboratory records only when necessary. The data will be collected by clinical staff as part of routine care on the BDNT and in the clinical records. Each BDNT is routinely kept in a file in the neonatal unit for ease of access, counting and notification of the cases with CDs. There is currently no electronic health record, computer database or storage options for the data in the BDNT.

For the study, each BDNT will be copied and anonymized by covering the patient's name and hospital number. A sequential study number will be allocated; for example, EDH BDNT 01/2018, EDH BDNT 02/2018, and so on until the last case is collected and entered on the database. These will be collated into a study file that will be kept in a locked office at the study site. No records will leave the EDH premises and the study file will serve as a back-up paper record for the unit. Thereafter, data from each BDNT will be entered and stored in a

password protected Microsoft Excel® workbook / database on the researcher's password protected laptop and / or hospital desktop computer. The workbook will also be stored on a password protected memory device to protect against damage and / or loss due to theft or computer malfunction such as virus infection. Data verification and catch-up data entry will be carried out monthly by the researcher/s to ensure good quality. It is anticipated that as the system is honed after implementation data collection may occur in real-time with same day data entry. This could be the pilot version of an electronic, real time CDs surveillance system with export of data monthly similar to morality audit systems like the Perinatal / Child Healthcare Problem Identification Program (PPIP / Child PIP).

The descriptive data analysis software package on Microsoft Excel® will be used and data will be presented in the forms of graphs and tables. Expert advice from an experienced researcher or a statistician will be sought as necessary. As this study is measuring a rate and describing the pattern of CDs, this is not anticipated.

The activities that are implemented to improve and maintain the quality of the data will be recorded as they occur and reported as a quality improvement (QI) activity.

3.6 Sample Size, Statistical Power and Variable Selection

The birth prevalence of CDs will be calculated as a rate per thousand live births or if large enough as a percentage. The number of live births with CDs and the total number of live births will be collected from the neonatal admissions register and births register respectively for the birth prevalence calculation. This will be a straight forward and accurate count of the live births and live births with CDs. The expected birth prevalence is between 1 to 3% live births, based on local knowledge and experience (Personal communication with Head of Neonatal Unit). This will yield a possible 3 to 6 cases of CDs per month. Therefore, a period of one year was selected for feasibility with available resources and time constraints and to achieve the study aim.

For the purposed of this study, a CD will be defined by international convention as: "a physical or anatomical abnormality detected at birth" and classified according to categories listed in Chapter XVII: Congenital Malformations, Deformations, and Chromosomal

Abnormalities of the International Classification of Diseases (ICD 10), 1997.

The variables to be described will be in two parts. The first will be the neonatal characteristics, including the date of birth, gender, gestational age and birth weight. The second will describe the pattern of CDs. The percentages of CDs in different diagnostic subcategories will be reported. For example, a neonate with Trisomy 21, a ventricular septal defect, and trachea-oesphageal fistula will be counted once in the overall birth prevalence rate and once in the subcategory for disorders of the chromosomal defect but not separately in all the subcategories such as chromosomal abnormality, circulatory system and digestive system.

If more information is required with respect to the pattern of CDs, the individual medical record will be consulted. A further breakdown into major and minor CDs and systems-based or interventions need categories may be used. This will be dependent on the data characteristics. A descriptive analysis of the data in the form of graphs, proportions and tables will be done.

4. ETHICAL CONSIDERATIONS

Participants

The participant group in this research study will be neonates identified with CDs. These study participants represent a vulnerable population, and all times during the study, the principles of beneficence, non-maleficence, distributive justice and autonomy will be practiced. To ensure confidentiality, no patient identifiers will be used in this study. All data obtained from the participants will be anonymized and a sequential study number allocated to protect the participants. Data will be copied from the BDNT, and no patient contact will occur, therefore individual patient consent will not be required. All precautions will be taken to protect the personal information of the patients and their families, and only the researcher/s will have access to the database.

Data Safety and Monitoring

The Birth Register, Neonatal Register and BDNT file are routine clinical registers that are part of normal hospital practice. They are maintained within their respective departments and

under staff controlled access. All written data that will be generated from this study will be maintained within a study file that will be kept in a locked office at the study site. No records will leave EDH premises and the study file will serve as a back-up paper record. Thereafter, data will be stored on a password protected MS Excel workbook / database on the researcher's password protected laptop and / or hospital desktop. This data will also be stored on a password protected memory device which will serve as a backup in case of damage and / or loss due to theft or computer malfunction. Following completion of the study, all data generated will be destroyed.

Independent Ethics Review

Ethical approval will be sought from a UKZN BREC committee and the site approval will be obtained from the hospital prior to performing the study.

Social Value

CDs are expected to emerge as a growing healthcare need in SA as the country undergoes its epidemiological transition. It will have a direct impact on the affected children and their families, as well as exert a huge financial burden on the country's health, education and social support services. The purpose of this study is to determine the birth prevalence and pattern of CDs in this study population, and hopefully highlight it as a growing current and future healthcare need requiring appropriate resources in SA.

5. STUDY LIMITATIONS

The study is a hospital based study, focused on determining the birth prevalence of CDs in the neonatal service at EDH. The study will unable to obtain a true population based measurement of CDs as out-born neonates will be excluded.

The recognition of congenital disorders will be limited by the skill of the healthcare workers at EDH. Major CDs, that is, those that are obvious at birth, for example a cleft lip, will be diagnosed more readily as compared to hidden defects such as renal or cardiac disorders. These less obvious diagnoses may be made after the child has left the unit, and this could impact on the results of the study. Under-reporting of CDs is a known problem at the study

site. This resulted in the a change of study design from retrospective to prospective, and prompted the initiation of a quality improvement (QI) plan to improve quality of data obtained.

The BDNT is a paper based method of data collection, and the quality of data obtained will be dependent on the compliance of healthcare workers. Illegible and incomplete forms may be encountered during the study. To overcome this limitation, individual clinical records will be consulted to obtain the required information.

6. FEASIBILITY

6.1 Timelines

- February 2018– Submit Protocol to PGC and BREC
- March/April 2018 – Obtain 1st BREC approval
- April 2018 – Obtain site and KZN DOH approval
- May/June 2018 – Final BREC approval
- July 2018 – Start Data Collection
- January 2019 – End Data collection
- February to April 2019 – Data analysis and draft write up
- May – June 2019 – Supervisor feedback and finalising dissertation
- July 2019 – Submit Dissertation and /or article publication.

6.2 Contributors and Authorship

Name	Department	Contribution
Dr M Z Saib	Paediatrics	Author
Dr BL Dhada	Paediatrics	Co-Supervisor
Prof C Aldous	Clinical Medicine	Supervisor

6.3 Study Funding

The researcher and supervisor will assume all costs, no external funding will be required. Anticipated costs include:

- Time of researcher and supervisors.
- Photocopying costs.
- Possible software training in MS Excel®, including data analysis function.

7. STUDY SIGNIFICANCE

Congenital disorders (CDs) are currently an unrecognized healthcare issue in South Africa. As a result, their contribution to the disease burden is underestimated, and the impact of interventions for their prevention and care is not being considered. As the country follows the epidemiological trend of industrialized nations, the contribution of congenital disorders to the disease burden will be expected to increase, until they eventually become the leading cause of childhood mortality and morbidity.

There is a lack of birth prevalence data for CDs. This is because of a lack of prioritization of CDs as a healthcare issue and a poor national surveillance system.

This study will aim to provide the birth prevalence and pattern of CDs at a regional hospital in SA. We plan to use the results to show how many and the types of CDs there are in this population to highlight the growing contribution to the disease burden and resource needs for SA children and their families.

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Appendix Two: Biomedical Research Ethics Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

10 December 2018

Dr MZ Saib (200303423)
School of Clinical Medicine
College of Health Sciences
zubbys@gmail.com

Protocol: The birth prevalence rate of congenital disorders among live births at a regional facility South Africa.
Degree: MMed

BREC Ref No: BE409/18

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received 12 July 2018.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 28 November 2018 to BREC correspondence dated 06 August 2018 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 10 December 2018. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 10 December **2018.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **11 December 2018.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Professor V Rambiritch
Chair: Biomedical Research Ethics Committee

cc postgraduate administrator: mbheles1@ukzn.ac.za Supervisor: Aldoussc@ukzn.ac.za

Appendix Three: Birth Defects Notification Tool

Birth defects notification form

Genetics reference number …… Code ……

1. GENERAL INFORMATION:-

a. Province …… b. District ……

c. Name of Hospital/Facility……

d. Facility/Ward telephone number …… f. Date ……/……/…….
day month year

e. Name of person notifying …… ……..

2. PARTICULARS OF MOTHER:-

a. Name …. . …… b. Date of birth/Age ……/……/…….
first surname day month year

3. PARTICULARS OF PATIENT (Please tick the appropriate block)

a. Surname …… b. First name ……

c. Gender Male Female Ambiguous d. Date of birth ……

e. Population group African White Coloured Asiatic Other Specify ……

f. Birth status Live Birth Still Birth Therapeutic Abortion Miscarriage

g. Birth weight <2500g ≥2500g h. Gestational age <37 weeks ≥37 weeks

4. PLACE OF BIRTH (Please tick the appropriate block)

a. Urban Hospital b. Rural Hospital c. Clinic d. Home e. Born before arrival

f.. Referred **to** another Hospital? Yes No g. Referred **from** another Hospital? Yes No

h. If yes, name of that Hospital ……

5. DIAGNOSIS:-

5.1 **PRIORITY BIRTH DEFECTS (Please tick the appropriate block)**

a. **Neural Tube Defects** Anencephaly Encephalocele Spina Bifida

b. Albinism c. Down Syndrome d. Tallipes equinovarus/club feet e. Fetal Alcohol Syndrome

f. **Clefts** Cleft lip & palate Cleft lip only Cleft palate only

Comments: ……

5.2 **OTHER BIRTH DEFECTS (Other birth defects that have not been included in item 5.1)**

a. Skull b. Face c. Chest d. Heart e. Abdomen f. Gastrointestinal Tract

g. Genitals h. Urinary System i. Arms j. Legs k. Hands l. Feet

Description ……

Section 5 completed by Doctor Registered Nurse **Additional Genetic Training** Yes No

6. INVESTIGATIONS REQUESTED (Please tick the appropriate block)

a. Chromosomal/cytogenetic b. Biochemical/metabolic

c. DNA/molecular d. No investigation necessary

e. Other diagnostic or screening procedure Specify ……

7. COUNSELING GIVEN (BY):- Please tick the appropriate block

Clinical geneticist Medical doctor Registered Nurse **Additional Genetic Training** Yes No

Genetic counselor No counseling given