AN INVESTIGATION INTO THE RENEWED NEED FOR THE CARE AND PREVENTION OF CONGENITAL DISORDERS IN SOUTH AFRICA

By

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Submitted in fulfillment of the academic requirements for the degree of

PhD

in the

School of Clinical Medicine

College of Health Sciences

University of KwaZulu-Natal

Durban

2017

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

Signed: _____ Name: _____ Date: ____

Dedication

This thesis is dedicated to my husband Arnaud and our children Amelie, Aiden and Nathan, and in loving memory of our daughter Madeleine. It is their support, encouragement and patience that made the completion of this study possible.

Declaration

I, **Helen Malherbe** declare that:

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

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Acknowledgements

My deepest gratitude and thanks to my supervisor Professor Colleen Aldous for your continued guidance, patience and encouragement throughout this study, including outside working hours! You somehow made this grueling, transformative process enjoyable.

To Professor Arnold Christianson, thank you for always having a ready answer for my questions and for the rich depth of insight you have shared so freely with me. It is a privilege to take the baton from you.

Thank you, Professor David Woods for your unfailing support, 24/7 assistance and for the unending practical wisdom, knowledge and encouragement that you have so willingly provided.

May the A-Team continue to change the world. It is an honour to stand alongside you.

Thank you, Professor Bernadette Modell for sharing your amazing database and for believing I could do it justice, you are an inspiration! Dr Matthew Darlison, without your encouragement and nuggets of wisdom I would not have made it.

Thank you to the College of Health Sciences, University of KwaZulu-Natal for the PhD scholarship awarded for the three-year period 2013-2015.

Co-author Contribution Statements

Designated authors meet all four criteria for authorship recommended by the International Committee of Medical Journal Editors (ICMJE) (1). This includes:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and
- Drafting the work or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Malherbe HL, Christianson AL, Aldous C. Need for services for the care and prevention of congenital disorders in South Africa as the country's epidemiological transition evolves. S Afr Med J. 2015;105(3):186-8.

This paper was conceptualized as a collective by the team, with a substantial contribution from Professor Christianson. The data interpreted in the article was collated by myself as the first author. As main author, I drafted the article and it was critically revised for intellectual content by both Professor Christianson and Professor Aldous. Both provided final approval of the article via email prior to journal submission. All three authors were involved in the minimal changes required by the journal in readiness for publication.

Malherbe HL, Christianson AL, Aldous C, Christianson M. Constitutional, legal and regulatory imperatives for the renewed care and prevention of congenital disorders in South Africa. S Afr J BL. 2016;9(1 MAY):11-7.

This paper was conceptualized by the team with detailed input from Professors Marylyn and Arnold Christianson. As main author, I undertook the desktop review and drafted the article. Critique of intellectual content was provided by Professors Marylyn and Arnold Christianson and Professor Aldous. Professor Aldous undertook the key task of reducing the article to comply with the journal requirements. All authors approved of the final version of the article submitted for publication via email and provided input for the prepared response and acceptance/rebuttal of the reviewer's comments to resolve queries prior to publication.

Malherbe HL, Woods DL, Aldous C, Christianson AL. Review of the 2015 Guidelines for Maternity Care with relevance to congenital disorders. S Afr Med J. 2016;106(7):699-71.

The initial idea for this paper was conceptualized by Professor Christianson in liaison with myself as the main author with other inputs from the other authors. I drafted the paper, which was critically reviewed by all other authors, who also provided email approval prior to submission.

Malherbe H, Aldous C, Woods D, Christianson A. The contribution of congenital disorders to child mortality in South Africa. In: Padarath A, King J, Mackie E, Casciola J, editors. South African Health Review 2016. Durban: Health Systems Trust; 2016. p. 137-52.

The initial concept for this chapter was a joint effort by myself and Professor Aldous, with design input from Professor Christianson and Professor Woods. The chapter was drafted by myself as main author with critique on intellectual content received from all authors. Particular assistance was provided on specific aspects by Professor Woods and Professor Christianson. All authors provided email approval of the chapter prior to submission and all provided feedback to resolve the reviewers input in finalizing the content for publication.

Malherbe HL, Aldous C, Christianson AL, Woods D. Contribution of congenital disorders to under-5 mortality. S Afr Med J. 2016;106(8).

This letter to the editor in response to an earlier article in the South African Medical Journal was the suggestion of Professor Woods. Following further input to develop the concept from the other authors, it was drafted by myself as the main author with inputs from all. Email approval was received from all authors prior to submission.

Malherbe H, Aldous C, Christianson A, Darlison M, Modell, B. Modelled epidemiological data for congenital disorders in South Africa. Health Policy and Planning (submission ready).

Conceptualization of this paper involved all the authors with differing degrees of input. Collation of the data was undertaken by myself as the main author. The Modell Global Database (MGDb) was shared by Professor Modell assisted by Dr Darlison. Data input, analysis and interpretation was undertaken by myself as main author. I drafted the text,

with critical intellectual inputs from all authors, who also provided email approval prior to journal submission.

Malherbe H, Christianson A, Woods D, Aldous C. The case for the genetic nurse in South Africa. Journal of Community Genetics. (Under Review).

Conceptualization of this article was a joint effort by all authors. As main author, I drafted the text and critical intellectual inputs were received from Professors Aldous, Christianson and Woods. All authors approved the final text prior to journal submission and provided input in response to reviewer feedback.

Darmstadt G, Howson C, Walraven G, Armstrong R, Blencowe H, Christianson A, et al. Prevention of congenital disorders and care of affected children: A consensus statement. JAMA Pediatr. 2016;170(8):790-3.

This consensus article was conceptualized by Dr Howson at the International Conference for Birth Defects and Disabilities in the Developing World held in Dar es Salaam, Tanzania in September 2015 with key inputs from the working group team of which I was a part. I was involved in the content design of the article throughout the course of the conference, and in drafting specific sections of the text with other key members of the group. I also provided critical feedback on the final text via email prior to submission along with all other authors.

Reference

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Abstract

Background

Congenital disorders (CDs) are a common, costly and critical health issue that are, as yet, unprioritised in South Africa (SA). Defined as abnormalities in structure or function present from birth, CDs are synonymous with birth defects. Although CDs are found in all populations, a greater proportion occur in middle and low income countries (MLIC), including SA, compared to industrialised countries.

Although serious CDs can result in death or lifelong disability, there is little recognition in SA of the burden of disease they represent. This is despite a global call in 2010 through World Health Assembly (WHA) Resolution 63.17 to prioritise CDs as a health care issue and to respond with specific actions to improve their care and prevention. The majority of CDs in SA remain undiagnosed or are misdiagnosed and if lethal, the cause of death is incorrectly assigned leading to underreporting and an underestimate of the true health burden. Key challenges include a lack of skilled clinicians to diagnose, treat and refer CDs, competing health priorities redirecting funding and human resources, and inadequate empiric data collated via national surveillance and monitoring. Despite the trend in industrialised countries where CDs are the leading cause of death in infants and children, there is little awareness in SA of the increasing proportion of deaths resulting from CDs as the infant mortality rate (IMR) decreases.

Medical genetic services offer care to those affected by CDs to reduce suffering and improve overall health by preventing CDs, collectively reducing the burden of disease. Since up to 70% of CDs can be prevented, cured or ameliorated through relevant interventions (including 40% that can be cured through mainly surgical correction and a further 30% where disability can be mitigated), medical genetic services are worthy of further attention.

Aim and Scope of Research

The aim of this study was to investigate the renewed need for the care and prevention of CDs in SA. The objectives of this PhD by publication were:

- To evaluate epidemiological transition related to CDs for the last 25 years in SA including its impact upon medical genetic services.
- Assess the existing constitutional and legislative framework relevant to CDs and medical genetic services in SA and its implementation.

- Highlight the contribution of CDs to child mortality and morbidity and the role of medical genetic services in obtaining significant further reductions in mortality.
- Develop modelled birth prevalence and outcomes for CDs in SA to highlight the contribution of CDs to the country's disease burden.
- Highlight the role of the genetically trained nurse as a key component in developing medical genetic services in SA and potential tools to develop this workforce.
- Demonstrate international consensus on the prevention of CDs and care of affected children with relevance to the Sustainable Development Goals (SDGs).

Structure and overview of the thesis

Paper 1 (Chapter 3) reviewed the current epidemiological context for CDs and medical genetic services in SA. Although the country is now back in positive epidemiological transition following the HIV/AIDS and concomitant TB epidemics, child mortality rates have stagnated since 2011 with no further significant reductions. This highlights the need to address other, unprioritised health issues, the first of which is CDs. With an IMR of 27 per 1 000 live births, SA is well past the stage of 40-50 deaths per 1 000 live births when countries should develop medical genetic services. SA is yet to recognise the growing health need represented by CDs, which will continue to rise as the country develops and the IMR decreases. Medical genetic services have declined as services for competing health priorities have developed, and SA is yet to respond to WHA 63.17 to prioritise the care and prevention of CDs.

Paper 2 (Chapter 4) outlines the international background and SA legislative framework for medical genetic services and their implementation. International, regional and national conventions, legislation, and policy were studied for relevance to CDs and medical genetic services and their implementation was evaluated, including a comparison of sector capacity between 2001 and 2015. A key finding was the specific provision for genetic services in the National Health Act 61 of 2003. Although a comprehensive legislative and regulatory framework exists in SA for the provision of medical genetic services, implementation has been fragmented and unsustained. CDs and medical genetic services are excluded from national strategy and interventions combating child mortality and non-communicable diseases (NCDs). Capacity in the sector today is at a lower level than in 2001. The underlying reason for the shortfall in implementation is the failure to recognise the burden of disease represented by CDs.

Paper 3 (Chapter 5) critiques the 4th edition of the Guidelines for Maternal Care in South Africa with relevance to CDs and medical genetic services. Disparate terminology is used for CDs throughout the guidelines and referrals to medical genetic services disregard the

insufficient capacity available for screening and diagnosis of CDs. This highlights the lack of consultation with the medical genetics sector during the development of the guidelines and demonstrates a lack of awareness around the growing health need and contribution of CDs to the disease burden in SA.

Chapter 6 is a book chapter that argues for recognition of the role of CDs in child mortality. With the reduction of child mortality a priority in SA due to Millennium Development Goal (MDG) 4, the contribution of CDs to child mortality is yet to be realized or acted on. Despite the lack of empiric data on CDs, mortality data is beginning to emerge in SA, with CDs overtaking infection as the 3rd ranking cause of early neonatal death in the Western Cape. In the context of stagnated child mortality, CDs need to be addressed if child mortality is to be significantly further reduced. Priority actions identified include increased political will and financial commitment, improved national surveillance, capacity building, community education and awareness, and the role of patient support groups.

Paper 5 (Chapter 7) continues with the focus on child mortality in a letter to the editor of the South African Medical Journal in response to published data on child mortality for a specific region of the Western Cape. The article data highlighted the limitations of the 10th Edition of the International Classification of Diseases (ICD-10) and the prolific use of the term congenital anomalies to represent the totality of CDs while excluding up to 40% of CDs. This contributes to underreporting and an underestimate of the true contribution of CDs to the disease burden.

In paper 6 (Chapter 8) the scale of the CD problem in SA is quantified through the development of modelled estimates of specific groups of early onset endogenous CDs for 2012. Modelled data enables informed policy making to proceed so that relevant services can be developed where observed surveillance is lacking. These modelled data provide the expected numbers of CDs, and as empiric data emerges, the need for modelling falls away. The Modell Global Database (MDGb) was adapted using SA demographic indicators to generate baseline estimates (in the absence of any care interventions) of CD birth prevalence. This was also a pilot of the MGDb used to develop national estimates based on locally sourced data in-country. Birth prevalence data for CDs with endogenous causes was sourced from well-established CD surveillance systems. Using the baseline estimates generated, the IMR was used to calculate access to optimal care/services. This was estimated at 30% in SA in 2012. The impact of services, including pre-pregnancy, pre-natal and post-natal treatment was found to considerably reduce mortality, and mitigate disability, dispelling the myth that *nothing can be done* for those affected with CDs. Owing to the increased number of survivors with disability, the number requiring care also increased. This highlighted the need for

a balance between the care and prevention of CDs as an integral part of medical genetic services.

In paper 7 (Chapter 9) the role of the genetic nurse in medical genetic services in SA was investigated. Current sector capacity is inadequate and required personnel targets for medical geneticists and genetic counsellors cannot be reached quickly enough to meet the growing health need even if relevant posts are designated. The history of the genetic nurse in SA, current shortfalls in genetic education curricula, and their potential future role in rebuilding genetic services in the country are outlined. The Medical Genetics Education Programme and the Congenital Disorders Handbook are proposed as potential tools to swiftly build capacity in nurses. The importance of integrating such capacity building into the relevant streams of the National Health Insurance (NHI) scheme is emphasized, which should occur in parallel to the long-term goal of increasing medical geneticists, genetic counsellors and the allocation of posts countrywide.

The final paper (Chapter 10) is a consensus document resulting from the 7th International Conference for Birth Defects and Disabilities in the Developing World held in September 2015 in Dar es Salaam, Tanzania. Developed by a core working group throughout the conference, it provides the global context for CDs including the Sustainable Development Goals (SDGs), World Health Assembly Resolution 63.17, and outlines a plan of action. Many of the global challenges and the subsequent priority actions highlighted in the paper are shared by SA.

Conclusion

The overall finding of this study is that there is an urgent need to renew medical genetic services in SA. Although these services have been shown to have an impact on reducing mortality and ameliorating morbidity, the country is well past the designated stage when such services should be developed. For child mortality to be significantly further reduced in SA, it is now a national imperative that medical genetic services in SA are renewed. This requires political commitment and accompanying financial resources.

Further modelling studies are recommended at the provincial level and for specific CDs in SA. This could be accompanied by the development of cost estimates for specific interventions to illustrate the socioeconomic impact and cost effectiveness of medical genetic services. Developing consensus in SA on the use of standardised terminology and definitions for CDs is necessary to ensure accurate reporting of CDs to reduce the underestimation of CDs to the disease burden.

Keywords: Congenital disorders; birth defects; epidemiological transition; medical genetic services; Modell Global Database; infant mortality rate; child mortality; disability; health surveillance and monitoring systems.

Acronyms

BDCT: Birth Defects Collection Tool

CD: Congenital disorder

Child PIP: Child Problem Identification Programme

CoMMiC: Committee on Mortality and Morbidity in Children

DOH: Department of Health

FAS: Fetal alcohol syndrome

G6PD: Glucose-6-phosphate dehydrogenase

GBD: Global Burden of Disease

HCP: Health care providers

HIV/AIDS: Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome

IMR: Infant mortality rate

LTHC: Long term health condition

NCD: Non-communicable disease

NNMR: Neonatal mortality rate

MDG: Millennium development goal

MGDb: Modell Global Database

MLIC: Middle and low income countries

MMR: Maternal mortality ratio

MRC: Medical Research Council

NaPeMMCo: National Perinatal Mortality and Morbidity in Children

NHA: National Health Act

NHI: National Health Insurance

PHC: Primary Healthcare

PPIP: Perinatal Problem Identification Program

SDG: Sustainable Development Goal

TB: Tuberculosis

U5MR: Under-five mortality rate

WHA: World Health Assembly

WHO: World Health Organization

Glossary of Terms

Birth defects: Abnormalities of structure or function, including metabolism, which are present from birth. Some birth defects are clinically obvious at birth while others manifest later in life. This term is synonymous with the term *congenital disorder* (1).

Birth prevalence: The number of infants who have or will develop a congenital disorder per 1 000 live births. Birth prevalence rates can be compared across populations, used to assess changes over time and in health burden projections (2).

Chromosomal abnormalities: Abnormalities in the number of chromosomes (monosomy, trisomy, mosaicism) or in the structure of chromosomes (e.g. deletions, translocations, duplications, inversions, insertion). Resulting loss or gain of genetic material causes physical and/or mental abnormalities (3). Trisomy 21 (Down syndrome) is one of the most common chromosomal abnormalities.

Communicable disease: Infectious or transmissible diseases, resulting from the infection, presence and growth of pathogenic agents.

Complex disorders: Congenital disorders/birth defects that develop after birth, some presenting in childhood but most manifesting in mid- or later life. Their aetiology requires an interaction between genes and, mostly postnatal, environmental factors. Common complex disorders include cancer, coronary artery disease, type-2 diabetes mellitus, hypertension, mental disorders and stroke (3).

Congenital anomalies: Macroscopic morphological anomalies present from birth. They exclude functional birth defects including non-syndromic, congenital disability (intellectual, physical, visual and auditory disability and epilepsy), common single gene disorders (e.g. haemoglobin disorders, G6PD deficiency, cystic fibrosis, oculocutaneous albinism, spinal muscular atrophy and inborn errors of metabolism. Also excluded are many common teratogen induced CDs including congenital syphilis, congenital rubella syndrome and iodine deficiency (1).

Congenital disorder: Any potential pathological condition arising before birth, including all disorders caused by environmental, genetic and unknown factors, whether they are evident at birth or become manifest later in life. This term is synonymous with the term *birth defect* (1, 4, 5).

Congenital malformation: The result of abnormal embryonic development of an organ or body part, causing a permanent defect because the underlying tissue is abnormal.

May be caused by chromosomal or single gene abnormalities, multifactorial conditions or teratogen exposure (3).

Genetic counselling: An education process used to inform individuals/families about the facts and implications of birth defects and complex disorders. The process is non-directive but also provides psychosocial support (3).

Genetic risk factors: Common gene variants that cause problems relatively rarely (2).

Infant mortality rate: The number of deaths of infants under one-year of age per 1 000 live births.

Maternal mortality ratio: The ratio of the number of maternal deaths during a given time period per 100 000 live births during the same time-period.

Medical Genetic Services: Care for those with a CD in order to reduce suffering and to improve health by prevention (6).

Multifactorial inheritance: The interaction of many genes with each other and the environment. Certain birth defects/congenital disorders follow multifactorial inheritance patterns, meaning that a person's particular genetic makeup (genotype) interacts with specific environmental conditions to cause the condition (3).

Neo-natal mortality rate: The number of deaths of infants under 28 days of age per 1 000 live births.

Non-communicable disease: A medical condition or disease that is non-infectious or non-transmissible.

Population prevalence: The number of affected individuals per 1 000 in a defined population. For congenital disorders this number is usually much less than birth prevalence because serious congenital disorders shorten life (6).

Serious birth defect/congenital disorder: A congenital disorder that is life threatening or has the potential to result in disability.

Single gene disorder: A disorder known to be caused by a single gene e.g. Cystic fibrosis.

Teratogen: An agent that can disturb the development of the developing embryo (first 8 weeks of life) or fetus during pregnancy. Teratogens include altered maternal metabolic states (diabetes mellitus, hypothyroidism, iodine deficiency), infectious agents, ingested substances (alcohol, illicit drugs and medications), hyperthermia, environmental pollutants and massive radiation exposure (3).

Under-five mortality rate: The number of deaths of children under the age of five years per 1 000 live births.

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Table of Contents

Chapter 1: Introduction

Background

Congenital disorders (CDs) are a common, costly and critical health issue which occur in all populations globally. The term *congenital disorder* is synonymous with birth defects which are defined as abnormalities in structure or function present from birth, including metabolic disorders, which may be diagnosed at birth or manifest in childhood or later in life (1). The majority of CDs are genetic or partially genetic in origin, with the remainder due to factors in the fetal environmental or a combination of these (2). There is an unequal distribution of CDs globally, with a greater proportion occurring in middle and low income countries (MLIC) compared to high income, industrialised countries (3). Serious CDs can cause death and those who survive may be disabled for life (3).

Although most countries worldwide are committed to reducing child mortality in response to the Millennium Development Goals (MDG), specifically MDG4, few interventions in MLIC targeted CDs specifically (4). This is despite the call in 2010 for World Health Assembly (WHA) member countries, including South Africa (SA), to prioritise CDs as a healthcare issue due to their contribution to child mortality, particularly neonatal deaths (5). The majority of deaths from CDs go undiagnosed or misdiagnosed - buried amongst mortality statistics from more obvious causes such as infectious diseases (eg. Diarrhea, HIV/AIDS, pneumonia, septicemia) (6, 7). It is not until countries control communicable diseases that mortality decreases, longevity increases and countries experience epidemiological transition, that the true burden of CDs is revealed (8).

Today, CDs are the leading cause of infant and child death in industrialised countries accounting for up to 28% of deaths (9). As overall child mortality decreased in these countries, the proportion of deaths from CDs increased. Medical genetic services have developed to care for those affected, incorporating prevention to minimize the number of affected births. In SA, an upper-middle income country, CDs are yet to be recognised as a priority health care issue. This is despite a considerable body of work internationally highlighting the need for medical genetic services to be developed at the community level in primary health care (PHC) for the care and prevention of CDs. With communicable diseases now decreasing in SA, and a parallel burden of non-communicable diseases (NCDs) emerging - of which CDs are the first - a greater emphasis must be placed upon developing medical genetic services.

A key reason for the neglect of medical genetic services in SA is competing health priorities, including HIV/AIDS and concomitant TB which have diverted political will and resources from CDs. The principal focus has been upon treating communicable diseases and other social determinants of health and it is these *low-hanging fruits* that are being responded to first, with little attention given to CDs (10). Many of these interventions aim at reducing the neonatal, infant and child mortality rate in SA, which has stagnated since 2011 (11, 12). Until CDs are tackled as a healthcare priority it is unlikely that the child mortality rate will be further significantly reduced.

In SA today, the majority of CDs remain undiagnosed or are misdiagnosed due to a lack of genetically trained clinicians and health care professionals, and inadequate infrastructure (3, 6, 13). Early, accurate diagnosis can prevent, cure or mitigate up to 70% of CDs (14). This includes curative surgical interventions for up to 40% of CDs (particularly congenital malformations) and in 30% of cases, the resulting disability can be ameliorated through rehabilitative or therapeutic treatments (6, 14). Many of the deaths occurring from undiagnosed and untreated CDs are preventable and the quality of life can be improved. Not all interventions to care and prevent CDs are expensive or high-tech – many are relatively low cost and can be integrated into existing health care programmes (3).

For those able to afford private healthcare services in SA, estimated at 16% of the population benefiting from 70% of all the doctors in SA working in the private sector (15), diagnosis and care of CDs is more likely, although not guaranteed. With 84% of the South African population dependent on state health care services, relevant and universally accessible services for the care and prevention of CDs are non-existent in most of the provinces (15).

With an infant mortality rate (IMR) of 27 deaths per 1000 live births in 2015 (16), SA is well below the threshold of 40 deaths per 1000 live births when medical genetic services should be implemented (6, 13, 17, 18). This urgently needs to be rectified.

Personal Motivation

Having lost a child due to a CD, the focus of this PhD is of personal interest and is the motivation for pursuing this area of study. Although we were able obtain a diagnosis and the best care available for our daughter prior to her death, we know that this is the exception rather than the rule in SA. A significant number of preventable deaths, unnecessary human suffering and huge socioeconomic cost are the result of the unethical shortfall in services. We have a responsibility to the most vulnerable of our society, our children and the disabled, to ensure that the most basic of human rights -

the right to life - is upheld by ensuring relevant, accessible medical genetic services are available to all South Africans.

Problem Statement

The research question asked in this study: *Is there a need for renewed medical genetic services in South Africa for the care and prevention of congenital disorders?*

There are a number of issues that have contributed to the decline of medical genetic services in SA and why there is now a renewed need for these services. The lack of recognition of CDs as a health care priority is the underlying reason, resulting from:

- **Confusion around CD definitions and terminology**: A variety of different, inequivalent terms are used interchangeably for CDs causing confusion, particularly for data reporting and comparison. Often, a sub-set of CDs is reported as the totality, which exacerbates underreporting.
- **Undiagnosed and misdiagnosed CDs:** Many CDs remain undiagnosed or are misdiagnosed, especially when comorbidity occurs. The more obvious condition, often secondary to the CD, is usually diagnosed, preventing the patient from receiving appropriate care. When death occurs due to a serious CD, the cause of death is often incorrectly assigned leading to underreporting.
- **Competing healthcare priorities and unaddressed healthcare issues**: the quadruple burden of disease in SA includes communicable diseases, NCDs, trauma and perinatal and maternal deaths. Combined with unaddressed social determinants of health this places a huge demand upon healthcare.
- **Lack of trained clinicians/capacity:** There is a severe shortage of relevant capacity in the medical genetics sector in SA (19). Without increasing this capacity it is not possible to respond to the increasing health need of CDs.
- **A lack of empirical data:** With little observed empirical data available in SA for CDs, there is little evidence that CDs are an issue requiring attention (20). Data sets held at health care facilities and registries held by patient support groups are currently not contributing to national surveillance.
- **Inaccurate assessment of the CD disease burden:** The underreporting of CDs leads to an inaccurate assessment of the contribution of CDs to the disease burden. With deaths and morbidity due to CDs being underestimated, this prevents the true situation from being realised.
- **Lack of political will & resources:** In the absence of an accurate estimate of the CD disease burden, obtaining political support and accompanying resources is a

challenge. This is despite global awareness and calls for prioritisation of CDs as a healthcare issue (5).

- **Lack of public awareness:** Public education and accurate public awareness is required to dispel myths around CDs to counter the stigma associated with CDs which has led to the unethical treatment of those affected by communities.

All these factors have contributed to the decline of medical genetic services in SA. Today medical genetic services are inadequate for the growing health need and those affected and at risk of CDs are not receiving the care they require and are effectively being marginalized, despite being, as children and the disabled, some of the most vulnerable of our society.

Rationale

The aim of this research project was to assess current medical genetic services at the macro-scale in SA to establish their relevance and adequacy in the current epidemiological context. Suggestions for improvements in services are made where appropriate.

Objectives

- To evaluate epidemiological transition related to CDs for the last 25 years in SA including its impact upon medical genetic services.
- Assess the existing constitutional and legislative framework relevant to CDs and medical genetic services in SA and its implementation.
- Highlight the contribution of CDs to child mortality and morbidity and the role of medical genetic services in obtaining significant further reductions in mortality.
- Develop modelled birth prevalence and outcomes for CDs in SA to highlight the contribution of CDs to the country's disease burden.
- Highlight the role of the genetically trained nurse as a key component in developing medical genetic services in SA and potential tools to develop this workforce.
- Demonstrate international consensus on the prevention of CDs and care of affected children with relevance to the Sustainable Development Goals (SDGs).

Structure of the thesis

This PhD by publication was a descriptive, desktop project including in-depth studies on several different sub-topics of relevance to medical genetic services for the care and prevention of CDs.

The literature review is included in Chapter 2 and is preliminary to the rest of the study.

The study comprises five parts. Excluding the discussion and conclusion, each part contains chapters which correspond to publications which are either published, forthcoming, currently under review or submission ready. The approach taken for each part is outlined as follows:

Part One: An overview

- **Chapter 3:** This paper outlines the epidemiological transition over the past 25 years. The impact of a counter transition upon medical genetic services related to the care and prevention of CDs and the increasing health need of CDs is highlighted. It includes an in-depth review of the literature and data collated and interpreted from secondary sources (demographic indicators and HIV prevalence of pregnant women), to demonstrate the current epidemiological context.
- **Chapter 4**: This paper reviews the constitutional, legal and regulatory provisions relevant to CDs in SA and their implementation. It outlines the existing legislative framework relevant to medical genetic services. A rigorous literature review was undertaken for this paper and each legislative or policy document identified was evaluated in detail for its relevant to medical genetic services and its role in the legislative framework. Implementation of current services was then assessed against this framework.
- **Chapter 5:** A critique of the 2015 guidelines for maternity care was undertaken with relevance to CDs and medical genetic referral services. This article was a response to national guidelines issued which have direct relevance to medical genetic services. The guidelines are compared with previous editions and the content evaluated against the current capacity available in the sector, highlighting the mismatch between what is being recommended and what may be possible.

Part Two: Congenital disorders and child mortality

- **Chapter 6:** This examines the role of CDs in child mortality and morbidity in SA. A comprehensive desktop review contextualizes the unaddressed health needs of CDs as a key reason for the ongoing stagnation of child mortality rates in SA. It reviews factors contributing to the underestimated role of CDs in the disease

burden, highlights gaps in medical genetic services and recommends future areas for development.

- **Chapter 7:** This letter to the editor in response to published child mortality data critically evaluates the use of terminology and definitions used to rank and categorise causes of death in a municipality of the Western Cape. It highlights the pitfalls of interpreting sub-sets of CDs as a totality, which can be misleading for the reader and also contributes to underreporting.

Part Three: Modelling data for South Africa

- **Chapter 8:** National and Provincial demographic indicators are used to adapt the Modell Global Database (MGDb) to the SA situation. By modelling birth prevalence and outcomes for some specific, early onset, endogenous CDs, their contribution to the disease burden can be better appreciated, despite the lack of empirical data in SA. This includes collating relevant local demographic data from within SA, with several sources investigated thoroughly prior to the identification of optimal data. A rigorous process of tailoring the MGDb to the SA context was undertaken using the collated data to generate modelled data. A process of data extraction, analysis and interpretation was undertaken and presented.

Part Four: Building capacity

- **Chapter 9:** This chapter discusses the role of the genetically trained nurse in medical genetic services. It includes a brief history of the genetic nurse in SA and an overview of the current shortfalls in genetic education curricula and their potential future role in rebuilding genetic services in the country using two specific training tools in the context of the National Health Insurance (NHI) scheme.

Part Five: Global consensus

- **Chapter 10:** This details consensus achieved at the 7th International Conference for Birth Defects and Disabilities in the Developing World in the context of the Sustainable Development Goals (SDGs) and World Health Assembly Resolution 63.17, and outlines a plan of action. This article required a diplomatic approach to ensure the balance of international and national priorities were appropriately merged and negotiated into an agreed format.

Discussion and conclusion

- **Chapter 11:** The discussion and conclusions chapter provides a synthesis of the entire thesis, including its novel contribution to the body of knowledge, and outlines recommendations for the improvement of renewed medical genetic services for the care and prevention of CDs in SA.

Limitations and Constraints

It was not the purpose of this study to provide a detailed audit of medial genetic services in SA but rather to provide a broad context for this growing health need. An overview of the current situation of medical genetic services is provided using available data, scientific literature and personal communications with recognised specialists in the area. Constraints include the lack of available empiric data on CDs in SA, requiring the development of modelled estimates, and best estimates were generated for capacity due as these figures could not be obtained from the National Department of Health.

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Chapter 2: Literature Review

Introduction

It is estimated that globally, 6% of live births are affected by serious congenital disorders (CDs) of genetic origin, and thousands more by CDs of post-conception causes (1). Serious CDs may result in death or disability (physical, visual, auditory, mental, behavioural or epilepsy) (1). CDs are caused pre-conception by genetic factors or partially genetic factors, or post-conception by abnormal environmental factors, including teratogens and by unknown factors (1-3). Although found in every population globally, CDs are not equally distributed and over 90% of CDs occur in middle and low income countries (MLIC) where 95% of CD related deaths also occur (1). The burden of CDs is often higher in MLIC than in high income countries, causing a heavier burden upon the families affected due to more limited resources available (1, 4-7). Reasons for this inequality include poverty, malnutrition, inadequate healthcare especially pre-and post-natal, high risk factors including a higher percentage of mothers of advanced maternal age and consanguineous unions, and selective advantage of some single gene disorders (1, 5, 7-9).

Definitions and Terminology

A variety of terms and definitions related to CDs have been used internationally throughout the literature, causing global confusion (10-12). In 2006 at a joint World Health Organization (WHO) and March of Dimes meeting, agreement was reached on the use of the term CDs as synonymous with birth defects. Defined as 'abnormalities of structure or function, including metabolism, which are present from birth', these may be obvious at birth or only manifest later in life (2). Despite this clarification, a variety of non-equivalent terms continue to be used for the gathering and exchanging of data on CDs in the literature, both in South Africa (SA), in other countries and by internationally collaborating organisations (2, 13-18). The most commonly used inequivalent term is *congenital anomalies*, which are macroscopic structural abnormalities[1] present from

[1] Congenital anomalies include chromosomal abnormalities, multifactorial malformations and some single gene defects. Excluded are all functional abnormalities including the haemoglobin disorders, glucose-6-phosphate dehydrogenase deficiency and oculocutaneous albinism, some single gene defects and post-conception disorders due to abnormalities of the fetal environment (e.g. fetal alcohol syndrome and congenital rubella syndrome) (11).

birth. As a sub-set of CDs, the term is used often throughout the literature, incorrectly, to represent the totality of CDs (2, 11, 12, 19-21).

The International Classification of Diseases 10th Revision (ICD-10) Chapter XVII Congenital malformations, deformations and chromosomal abnormalities, collectively comprises congenital anomalies and has contributed to this interchangeable use of non-synonymous terms (2, 17, 22). Many epidemiological studies and other research groups report on congenital anomalies using the ICD-10 Chapter XVII. Many other CDs are found elsewhere in the ICD-10 system, including single gene disorders and inborn errors of metabolism (e.g. oculocutaneous albinism), blood disorders (e.g. haemophilia) and environmentally caused CDs (e.g. fetal alcohol spectrum disorder), collectively accounting for an estimated 40-50% of CDs (12, 18, 23). The Global Burden of Disease (GBD) includes six categories of congenital anomalies only (23-25). As a result, CDs are underestimated by the GBD according to Sitkin (2015) (25) and 'do not feature prominently in the overall health burden' as highlighted by Bittles in 2013 (23). The World Health Assembly Resolution 63.17 recommended widening the scope of congenital abnormalities in the ICD classification during the 11th revision, which is due for completion in 2018 (18).

In SA, a variety of terms have been used to describe CDs. The majority of the SA scientific literature refers to congenital anomalies (based on the ICD-10 classification) even when an alternative term, such as congenital abnormalities is used (13, 16, 21, 26, 27). The lack of standardised CD terminology in SA has led to considerable confusion, as demonstrated by the 14 different terms used interchangeably in the 2015 Guidelines for Maternity Care (14, 28). Some programmes, such as the Child Perinatal Problem Identification Programme (Child PIP), are beginning to address this issue (29).

As for many MLIC, empirical data are lacking for CDs in SA, preventing accurate birth prevalence and stillbirth rates being known for many conditions and requiring the use of modelled estimates (1, 5, 7, 18, 30-32). An estimated minimum of 1 in every 15 live births or 6.8% are affected by a CD in SA (33). This is double the rate reported in high income countries such as the USA, where 1 in 33 or 3% of live births are affected (34). Although less births are affected by CDs in high income countries, CDs account for a greater proportion of infant and child death, and disability in high income countries. In 2013 in the USA, congenital malformations, deformations and chromosomal abnormalities were the top-ranking cause of death, accounting for 20% of mortality in infants (35). When categorised according to the World Bank levels of Gross National Income (GNI) classification, 28% of deaths were attributed to children under-5 due to CDs in high income countries in 2013 (36). In comparison, for upper middle income countries such as SA, 14% of under-5 deaths were attributed to CDs in the same year,

having risen from 9% in 2000 (36). For SA, the national figure of under-5 deaths due to CDs was 6% in 2013, despite SA being an upper middle income country (36).

Epidemiological Transition

The proportion of child mortality attributed to CDs is indicative of a country's stage of epidemiological transition and development, as demonstrated by the 2015 World Health Statistics (36). As a population's health status improves, the infant mortality rate (IMR) decreases and the contribution of CDs increases (5). The stage of epidemiological transition at which a country is required to develop medical genetic services has been designated at an IMR of between 40-50 per 1 000 live births (7, 8, 19, 37, 38). It is argued that this is the point at which infectious diseases are being adequately controlled, enabling a greater focus on non-communicable diseases (NCDs), including CDs (30, 38). For many MLIC this is not occurring, as outlined in the next section.

Industrialised, high income countries followed Omran's classic three-stage, linear, unidirectional model of epidemiological transition (39). As communicable diseases were controlled and eradicated, mortality and fertility decreased, life expectancy at birth increased, and non-communicable and degenerative diseases emerged (39). The eradication of communicable diseases revealed the previously hidden burden of CDs, which attained public health significance in these countries in the early 1960s (1, 40). Although Omran's original concept included a contemporary delayed model for developing countries, it made several assumptions, including homogeneity in MLIC. A considerable body of research has shown this model to be too simplistic and inflexible for MLIC, which are a diverse group of countries (1, 5, 30). In these MLIC, transition stages often overlap, are reversible (leading to a counter transition) and are not completed, resulting in coexistence of different types of disease in the same population (41-43). This has resulted in Omran's model being modified with two further stages being added, including stage five 'the age of emergent and re-emergent infections' (41, 42, 44-46).

Epidemiological Transition in South Africa

Epidemiological studies in SA, including reports from the Agincourt Health and Socio-Demographic Surveillance System, indicate that the country is undergoing a protracted epidemiological transition and has experienced a counter transition similar to the experience of other Sub-saharan African countries (43, 46-49). After steadily decreasing since the 1960's (47), overall mortality began to rise again in the late 1990's due to the

emergence of HIV/AIDS, the resurgence of TB and the simultaneous increase in non-communicable disease – resulting in a double burden of disease (26, 43, 48, 50).

Epidemiological polarisation has also been demonstrated in SA, with different social classes experiencing different types of disease, mortality and morbidity rates exacerbated by apartheid history and unaddressed social determinants of health (21, 23, 41, 43, 46, 47, 51, 52). The impact of highly active antiretroviral therapy (HAART) made universally available in mid-2004, and prevention of mother-to-child HIV transmission (53) is outside the scope of the published Agincourt studies, for which data cause-specific mortality has been published up until 2004. These and other interventions contributed to significantly reducing infant and child mortality and increasing longevity from 2008 until 2011, returning the country to positive epidemiological transition as highlighted by the Rapid Mortality Surveillance Reports (54-56).

In SA the double burden of disease has been contextualised as a quadruple burden which includes HIV/AIDS, injuries and violence, chronic diseases and poverty related diseases (26, 57). Poverty related diseases are a collective of communicable diseases, NCDs, trauma, and unaddressed social determinants of health (7, 57), later revised to perinatal and maternal deaths, most likely in response to the Millennium Development Goals (MDGs) (58). In SA, as for other MLIC, persisting communicable disease and emerging NCDs continue to bury CDs, and they are yet to be prioritised as a health care issue in public policy (59, 60).

The first non–communicable disease

While NCDs are now included in national priorities and strategies in parallel to a continued focus on communicable diseases - CDs are excluded. CDs are not being contextualised as an NCD in these national documents (61), despite other national (21) and international organisations, including WHO, categorising them as such (61-63). Examples include:

- The DOH Strategic plan for the Prevention and Control of NCDs 2013-2017 (64). This focuses upon a healthy lifestyle which addresses the risk of tobacco use, physical inactivity, unhealthy diets and alcohol abuse. Genetic factors are specified only once in the document as a determinant of disease with no further details or interventions outlined.
- The DOH Strategic Plan for Maternal, Newborn, Child and Women's Health (MNCWH) and Nutrition in South Africa (59). This specifies that chronic and long-term health conditions affect 15-20% of children, highlighting current

inadequate services and care for these children but does not connect this to the 8% of neonates dying in SA from congenital abnormalities also mentioned.

- Reports of the Committee on Morbidity and Mortality in Children under-5 years (61, 65). CDs are included under 'long-term health conditions' (LTHC) which is a newly defined collective term to cover chronic diseases and disabling conditions, including both genetic and acquired conditions (61, 63). In this context, the term NCDs are not considered applicable for childhood, which is in contradiction to global consensus on the topic (61, 63).

The Millennium Development Goals

The MDGs set in 2000, specifically MDG4, initiated a global drive to reduce child mortality (58). A positive impact was seen in most countries, with child mortality being reduced globally by 53% by the deadline, annually saving 6.8 million children's lives between 1990 and 2015 (66). SA experienced a poor start as one of only four countries globally that experienced an initial rise in under-5 mortality after the MDGs were set (53). Only after child mortality was integrated as a strategic health priority and various interventions were implemented, did child mortality began to decrease once again (53, 67). Although MDG4 was not reached by the end of 2015, a reduction of one third in U5MR was achieved in SA, with dramatic reductions seen until 2011 (54, 55).

Although the MDGS resulted in a focus upon saving the lives of babies and children in SA, as evidenced by the appointment of several Ministerial Committees (61, 65, 68), the contribution of CDs to the burden of disease is yet to be recognised. Efforts are underway to address social determinants of health, most notably the 11 interventions reported by Chola *et al* (69) to further reduce child mortality. These exclude specific interventions related to the care and prevention of CDs, which may potentially enable further significant reductions, particularly during the first year of life (29). An analysis of the contribution of CDs to child mortality in SA is needed, supplemented by evidential data to highlight the burden of CDs, such as empiric, observed data collected through surveillance and monitoring.

Surveillance and Monitoring of Congenital Disorders

Global monitoring of CDs began in the late 1960s following the thalidomide epidemic to prevent a repeat of this tragedy (70). In 1974, the International Clearinghouse for Birth Defects Monitoring Service was founded with a focus on monitoring and to ensure accurate counting (71). This was renamed the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) in 2005 with a new emphasis on surveillance

– the analysis and interpretation of collected data to plan, implement and evaluate public health interventions in response (1, 70, 71). An analysis of the ICBDSR Annual Report for 2014 demonstrates that of the 42 monitoring systems contributing data that year, 31 were from high income countries, 9 from middle income countries (7 upper middle and 2 lower middle income), with no low income countries contributing data (72). The predominance of high income countries reflects their early commencement of monitoring more than 40 years ago, in parallel to their early epidemiological transition (70). Implementation of monitoring and surveillance by MLIC has occurred more recently and is still lacking in many MLIC, particularly those experiencing a protracted epidemiological transition (23, 41, 43). With little empiric data in MLIC, the true burden of disease from CDs is being underestimated and unrecognised (30). This is despite repeated global calls for improved surveillance and monitoring in MLIC over several decades (2, 4, 5, 7, 9, 18, 19).

In SA, the first documented birth defects surveillance system was initiated in the Cape Peninsula in 1982 as reported by Sayed *et al* (73). However, data collected via this system was deemed unsuitable for surveillance purposes by the local health authorities due to gross underreporting (73). Two tools were then developed: a birth defects surveillance system and a genetics postnatal congenital form – the former used for recording CDs identified at birth and the latter for use at any age (74).

In 2004 the decision was taken to develop a single standardised tool, and the Birth Defect Collection Tool (BDCT) was implemented from mid-2006, administered by the National Department of Health (74). Recent work by Lebese *et al* (75) on data collected via the BDCT from 2006-2014, indicates underreporting of CDs in SA by over 98%. Although additional CD data are collated at some facilities and for patient registries by patient support groups, these are not integrated into national surveillance (David Woods, Personal Communicaton). Without these empirical data it has not been possible to accurately establish prevalence rates for specific CDs in SA, or an overall estimate of the CD burden.

Modelling

The lack of empiric data on CDs, particularly in MLIC has led to the development of modelled data for CDs. In 2006 the March of Dimes Global Report on Birth Defects included a summary of the Modell Birth Defects Database (MGDb) with the first global estimates of birth prevalence data for serious genetic/partially genetic birth defects (1). This used data from well-established surveillance systems and registries with stable data over an extended period verified with other sources to generate baseline estimates of

country-specific birth prevalence (1). The accuracy of the modelled data is dependent on the quality of the available literature and demographic data inputs. For SA, the MGDb estimate was 53.4 genetic/partially genetic CDs per 1 000 live births, excluding post-conception environmentally caused CDs (1). The publication of these data caused significant international interest resulting in a joint March of Dimes-WHO meeting a few months later, where these global estimates were endorsed (2). The MGDb is currently undergoing a process of updating and revised global estimates based on updated modelling (12).

In SA there is a limited body of work on the prevalence of CDs, particularly for some of the priority conditions (76) including Down syndrome, albinism, fetal alcohol syndrome (FAS) and NTDs (77-98). Developing additional modelled estimates could provide a useful interim measure for these and other CDs. Provincial level estimates may also help overcome a current limitation of the MGDb by allowing for heterogeneity of populations (23).

Training of Health Care Professionals

For CD's to be reported via a monitoring and surveillance system, they must first be identified and diagnosed. A key reason for underreporting in MLIC is the lack of trained clinicians and facilities available to accurately diagnose CDs (1, 2, 5, 27, 30, 89). Consequently, in MLIC, CDs are often undiagnosed or misdiagnosed resulting in the patient's early death (7, 10, 25). These deaths are absorbed into mortality statistics for communicable diseases, malnutrition or prematurity, contributing to the underreporting of CDs (1, 4, 6, 7, 25, 30, 89, 99-102). There is a complex interplay between CDs, prematurity and other pathologies with some infections causing CDs, while some CDs may lead to increased risks of developing other severe infections (4, 101). Lack of diagnosis, co-morbidity and underreporting are all acknowledged as factors in relation to CDs in SA (65).

Several key factors have contributed to the lack of trained clinicians available to identify and diagnose CDs in SA. The global shortage of doctors, including specialists, is keenly felt in the country (103, 104). Only 12 medical geneticists are currently practicing in SA (1 per 4.6 million of the population), which is less than half the recommended number of 27 (1 per 2 million) based on the current population (105-108). With medical genetics designated a primary specialty in 2007 and requiring an additional four years of training, increasing capacity will take time even if the required funding and posts are made available (109). If SA is to take advantage of the advances in genetics and genomics and integrate these into health care services more rapidly, appropriate genetics training of

all health care professionals needs to be considered (37). Recent studies have highlighted the need to improve genetics content in nursing curricula in SA (110-113) and this sentiment is echoed in the international arena (37). The key role of genetically trained nurses in medical genetics services in the past (114) needs to be investigated once again, along with possible tools to build up the required workforce as rapidly as possible. Long-term measures are needed to equip all health care workers appropriately during training by addressing the shortfalls in medical, nursing and allied health care professions curricula (5) and continuing genetics education for those already in clinical practice (76).

Medical Genetic services

Medical genetic services are defined as health measures to 'help people with a genetic disadvantage to live and reproduce as normally as possible' (1, 4, 5, 8, 30). For individuals, these provide for medical and psychosocial needs of those affected or at risk of CDs and to maximise offspring free of genetic disease. This includes early and accurate diagnosis, long-term and anticipatory care, and genetic counselling and psychosocial care (4, 5, 10). At the population level, public health measures to reduce the burden imposed by CDs include primary, secondary and tertiary prevention (care) (1, 5, 8, 30).

Medical genetic services develop when CDs are perceived as a significant health problem, usually when the IMR drops between 40-50 deaths per 1 000 live births (4, 7, 8, 37, 38, 51). This mounting health burden of CDs occurs in parallel to infectious and nutritional diseases, which persist as the main cause of death while the IMR is still above 25 per 1 000 live births (51). It is only once the IMR drops below 20 per 1000 live births that CDs emerge as the leading cause of infant death (19). Reducing the IMR to less than 10 per 1 000 live births requires optimal medical genetic services for the care and prevention of CDs to be in place (4). In 2015, the SA IMR was estimated at 27 per 1 000 live births (55, 56).

Interventions for CDs

As deaths from CDs become visible in a country's mortality statistics, there is often a delay in acknowledging their proportionate increasing role in mortality and morbidity (13, 16, 17). In MLIC, medical genetic services, particularly surgery for those affected by CDs, continue to be perceived as an unaffordable luxury (4, 11, 115, 116). In some cases, there is blatant apartheid of providing treatment to children with communicable diseases above those with CDs (11, 30). As outlined by Christianson (11), this

marginalisation and discrimination of people with CDs, many of whom are children and disabled, diminishes their human dignity and denies their basic human and constitutional rights.

In 1993 groundbreaking work by Czeizel (117) demonstrated that although 30% of those affected by serious CDs will die regardless of intervention, up to 70% of the CD burden can be prevented or treated (2, 10, 30, 118). For 40% this includes lifesaving or curative treatment - mainly through surgical intervention for conditions such as neural tube defects (NTDs), club foot, cleft lip and/or palate, congenital heart disorders (CHDs), undescended testicles, gastrointestinal tract abnormalities etc (10, 117, 119). For the remaining 30%, rehabilitative or long-term therapeutic treatment can mitigate disability enabling improved quality of life (10, 30, 37, 117). This work has gone relatively unheeded by many MLIC, including SA, as evidenced by the lack of prioritisation of medical genetic services (120).

An overwhelming body of work has emerged in the literature highlighting the role of paediatric surgery as a cost effective tool in reducing the burden of surgically avertable CDs (mainly congenital malformations) in MLIC (25, 121-124). Work by Higashi *et al* (2013)(121) demonstrated that 12.7 million (59%) disability-adjusted life years[2] (DALYs) are avertable with full surgical coverage for NTDs, CHD and cleft lip and/or palate. Paediatric surgery has been shown to be as cost-effective as vaccines and infectious-disease treatments and thought to be cheaper than condom distribution (115, 116, 125-127). Despite these studies demonstrating the cost effectiveness of surgical intervention, the lack of qualified surgeons in MLIC, including in SA, is a key stumbling block (25, 29). Building up local surgical expertise offers a more affordable and sustainable long-term solution than the high cost of repeatedly bringing in external expertise through vertical programmes (124). Surgical and other intervention also has implications for reducing morbidity, since many of those affected by CDs survive with disability (1). The 1997 South African Integrated National Disability Strategy (128) highlighted that the majority of disabilities are preventable, and that prevention must be a cornerstone of disability policy. However, to date there is no national prevention policy for disability (129) and existing policies and strategies are poorly coordinated with disability under-prioritised, resulting in those living with disabilities, including those resulting from CDs, not having access to the rehabilitative and other services they require (130).

[2] Disability-adjusted life years (DALYs) are metrics used for measuring the disease burden in terms of mortality and morbidity. One DALY is one healthy year of life lost due to disability or premature death.

Care and prevention

A further issue for consideration when developing medical genetic services that emerged during this literature review is the balance between the care and prevention of CDs. Although both must be implemented, the emphasis in many MLIC tends to be upon prevention only, as highlighted in the March of Dimes Global Report on Birth Defects (1). The issue of over emphasising prevention, specifically termination of pregnancy (TOP) for severe prenatally diagnosed CDs, was highlighted during this PhD study by reviewers providing feedback on submitted articles. The emphasis on TOP as one specific preventative intervention solely for economic reasons ignores the need for relevant and accessible care for those affected, which is unethical and echoes eugenic sentiment against the infirm seen throughout history (11, 51). The mantra of Christianson 'Care is an absolute, prevention is the ideal' (131) demonstrates the integrated approach required in medical genetic services – advocating that care of those affected must come first. This is confirmed by WHO international expert consultations which define the control of CDs as 'an integrated strategy combining the best possible patient care with prevention by community education, population screening, genetic counselling and the availability of prenatal diagnosis' (1, 4, 5, 8, 118). While care is the first objective, it must be balanced with prevention since the cost of care will rise as more patients survive (1, 30, 37). The implementation of primary prevention (ensuring individuals are born free of CDs through normal conception and preventing damage in utero)[3], secondary prevention (minimizing the number of children born with CDs)[4] and tertiary prevention (early detection, cure and amelioration of problems once a child is born with a CD)[5] – which is essentially care, comprehensively integrates these two concepts (1, 30).

Although medical genetic services in industrialised countries developed decades ago as these countries completed epidemiological transition, the resulting services available are far from ideal (1). These services were initiated by specialists in a range of disciplines, resulting in fragmented tertiary services with no unified strategy and little contact with public health or community-based services (30, 132). Medical genetic services in these industrialised countries are characterized as highly specialized, technical and expensive, focusing on 'controversial aspects of diagnosis, treatment and prevention' functioning

[3] Primary prevention is achieved through family planning, optimizing women's diets, managing maternal infections (e.g. rubella, syphilis, toxoplasmosis) and illnesses (e.g. diabetes mellitus and epilepsy), pre-conception screening for common recessive disorders (1).

[4] Secondary prevention is achieved through medical genetic screening and prenatal diagnosis, genetic counselling. therapeutic options and the option of termination of pregnancy (1).

[5] Tertiary prevention or care interventions include early recognition and diagnosis (e.g. newborn screening), medical treatment of complications, surgical repair of congenital malformations, neurodevelopmental therapy for those with disability and palliative care for those dying as a consequence of their CDs.

from academic centres in urban centres with limited access in rural areas (30). There has been a tendency for MLIC to follow this model (120) although a different approach is recommended for developing these services in these countries (1, 4, 5, 7, 30, 118). Integrating medical genetic services into existing primary healthcare programmes (PHC), with referrals for complex cases, should be the aim for MLIC rather than vertical programmes (4-6, 10, 37, 118).

Medical genetic services in South Africa

Limited medical genetic services are documented as far back as the 1950's, and were integrated as a part of the state funded health services through the National Health Act (63 of 1977) (51, 109, 114, 133). Operating from research-oriented urban academic centres (38, 51), these followed a similar approach to that taken by industrialised countries. Only a small portion of South African society was reached, mainly the affluent whites for whom CDs were a perceived health priority, experiencing similar epidemiology to that in developed countries, as outlined by Jenkins (38, 51). Although these services were only available for a portion of the population, budgetary constraints were already cited as a limitation of developing these services further (51).

Momentum in developing medical genetic services in SA began in the mid to late 1990s, as mortality decreased and longevity increased and the country began to transition epidemiologically (38). The IMR reached a low point in SA of 46 deaths per 1000 live births in the 1990s (134). This prompted a committee to be established by the National Department of Health, chaired by Prof H.M. 'Jerry' Coovadia to investigate primary health care services for women, maternal and child health in SA, including services for the care and prevention of CDs (Arnold Christianson, personal communication). Soon after, a national task force of experts was established in collaboration with the WHO to investigate the need for, and implementation of, services for the care and prevention of CDs. Following wide consultation, the National Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities were published in 2001 (76). Three years later, the National Guidelines for the Care and Prevention of the Most Common Genetic Disorders, Birth Defects and Disabilities followed (135). The Medical Genetic Education Programme was developed and began implementation in 2003. However, the competing health priorities of HIV/AIDS and concomitant TB diverted attention and resources from CDs, leading to their neglect over the following decade. The 2013 Capability GenTEE report (120) highlighted SA as the only country out of eight emerging countries evaluated where positive development in improving medical genetic services has ceased, and has actually regressed.

In 2010 World Health Assembly Resolution 63.17 (18) highlighted the role of CDs in neonatal mortality and urged member states to address CDs as a priority health issue to achieve MDG4. SA is a United Nations member state and required to respond to this resolution, but is yet to do so. Following the appointment of a democratically elected government in 1994, substantial legislative and policy changes were made to redress past inequalities, including the Constitution of South Africa (Act 108 of 1996) (136) and the National Health Act (61 of 2003) (137). The HIV/AIDS and TB epidemics occurring simultaneously with these policy changes significantly impacted medical genetic services, which were integrated into PHC as part of this policy revision process (138). To date, no detailed study of legislation and regulation with relevance to CDs has been undertaken in SA, which is required to identify shortfalls in implementation and service delivery.

Conclusion

In 1990, Professor Trefor Jenkins predicted that 'with greater emphasis on PHC and preventative medicine, the IMRs among the present underprivileged populations, including those in rural areas, will drop and the demand for genetic services will increase' (51). For the reasons outlined in this literature review, more than 26 years later this is still to be fully realised.

A defined approach on how to develop medical genetic services for the care and prevention of CDs is clearly documented in the available literature (4, 5, 7, 9, 19). These recommend the integration of genetic services into PHC as part of ongoing health programmes, an issue which many industrialised countries are now grappling to address through their established fragmented services. The key components of medical genetic services recommended for MLIC include accurate monitoring and surveillance of CDs, public awareness, education and training of healthcare providers; and political commitment including funding (1, 5, 6, 30, 37). These interventions do not need to be initiated simultaneously, nor are they all expensive and high-tech. There is however, a high societal cost of inaction both to public health (socioeconomic) and avoidable human suffering which is often ignored (5). The 'best possible patient care available needs to be provided in the existing circumstances' (1) which may differ within and between countries but will improve as resources and commitment are increased.

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Part One: An Overview

Part One provides the context for congenital disorders (CDs) in SA. General themes that emerge include the lack of empirical data for CDs which has prevented their true contribution to the disease burden from being inaccurately assessed; and as for many middle low income countries (MLIC), CDs have remained buried as a healthcare issue in SA due to other health care priorities. Although there is an existing framework of legislation that provides for medical genetic services in SA, there is incomplete implementation. This is mainly due to a lack of infrastructure and capacity – skilled clinicians to diagnose, refer and treat those affected to meet the current and growing health need. Part One is divided into three chapters:

Chapter 3 'sets the scene' and outlines the overall incidence (birth prevalence) of CDs in SA and reviews epidemiological transition in SA over the past 25 years. This reveals that SA has not followed the classical stages of Omran's theory (1) of transition due to the HIV/AIDS and concomitant TB epidemics. Although the country is now back in positive epidemiological transition, medical genetic services are inadequate to meet the growing health need. It is predicted that the proportion of child and infant deaths from CDs will increase in SA as communicable diseases are better controlled, following the trend of industrialised countries. Child mortality rates have stagnated in SA since 2011 (2, 3), suggesting unaddressed health issues – such as CDs that need to be prioritised.

Chapter 4 evaluates the existing framework of legislation relevant to CDs and the provision of medical genetic services. The idea behind this article was to find out what the government is doing in response to CDs through the development and implementation of medical genetic services. The results of a desktop review highlight the international protocols, national legislation and policy documents and national guidelines of relevance to medical genetic services. A considerable number of new laws were introduced post-1994 and there is provision for comprehensive genetic services, particularly in the National Health Act (Act 61 of 2003) (4) and the Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities in 2001 (5). However, despite this theoretical provision, there has been a shortfall in practice and medical genetic services have declined in recent years. Capacity in the sector is now lower than in 2001. Key reasons for this are suggested as a lack of political commitment, funding, post allocation and general lack of prioritisation of human genetics as a health issue and the disease burden represented by CDs.

Chapter 5 is an article in response the new edition of the 2015 Guidelines for Maternity Care (6) with relevance to CDs. This follows on from the previous chapter by demonstrating that emerging policy is disconnected from the current reality of the medical genetics sector. In comparison to the previous issue of the guidelines, this document uses a wide range of inconsistent terminology to represent CDs. This highlights a lack of insight and awareness of issues related to CDs. A number of recommendations made in the guidelines for referrals to medical genetic services are theoretically correct but are implausible in practice due to the lack of current capacity in the sector. No attempt was made during the development of the guidelines to collaborate with the medical genetics sector.

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Chapter 3: Need for services for the care and prevention of congenital disorders in South Africa as the country's epidemiological transition evolves

This article has been published in the South African Medical Journal.

Malherbe HL, Christianson AL, Aldous C. Need for services for the care and prevention of congenital disorders in South Africa as the country's epidemiological transition evolves. S Afr Med J. 2015 Mar;105(3):186-8. doi:10.7196/SAMJ.9136.

Need for services for the care and prevention of congenital disorders in South Africa as the country's epidemiological transition evolves

The lack of prioritisation of congenital disorders (CDs) in healthcare, and the limited resources allocated to prevention and to the care of those affected, is an issue of global concern. This is especially true in low- and middle-income countries (LMICs), where over 90% of CDs currently occur, resulting in 95% of CD deaths worldwide.[1,2]

In 2010 the World Health Organization's World Health Assembly (WHA) prioritised services for the care and prevention of CDs, particularly in LMICs, by passing Resolution WHA63.17.[2] This recognised the importance of CDs as a cause of stillbirths and neonatal deaths, their contribution to under-5 mortality, and their contribution to failure to attain Millennium Development Goal 4 (MDG4). WHA63.17 urged member states to recognise and address CDs as a public health issue. It also highlighted the lack of accurate epidemiological data available for many LMICs.[2] CDs are often undiagnosed or misdiagnosed and the cause of death wrongly attributed. Collectively, this prevents policy decision-makers from correctly assessing the burden of CDs in these LMICs.[3]

In South Africa (SA), the constitutional, legal and regulatory framework exists to promote the development of services for the care and prevention of CDs. It is the government's responsibility to provide such services. To understand the renewed need for these services, it is important to consider, contemplate and review the epidemiological transition that has occurred in SA over the last 25 years.

Epidemiology of CDs in SA

Modelled data of genetic causes of CDs[1] and an estimate of teratogenic causes (A L Christianson, personal communication, 2014) indicate that a minimum of 6.8% of births, representing one in every 15 live births in SA, is affected by a CD. Of these, 80.5% are genetic or partially genetic in cause, while 19.5% are caused by teratogens. The latter is higher than the 10 - 15% expected, owing to the high prevalence of fetal alcohol syndrome.[1] With 26.2% of CDs diagnosable in the first day of life, over 18 000 cases annually should be identified and reported in SA.[4] However, in 2012 only 2 174 CDs were reported via the Birth Defects Collection Tool administered by the National Department of Health (NDoH) (V Mtyongwe,

personal communication, 2013). This indicates under-reporting of 88%!

Although serious CDs can be life threatening or result in long-term disability, up to 70% can be prevented, cured or ameliorated by appropriate care.[1,5] Many interventions are relatively inexpensive and low-tech, including surgery for congenital malformations and community-based preventive measures (e.g. iodine and folic acid fortification of staple foods).[1]

Epidemiological transition

Epidemiological transition is the term for the change in population health statistics and pattern of diseases of a country or region, consequent on change in socioeconomic, education, infrastructure and healthcare development.[1] Omran's three-stage model of epidemiological transition[6] has been used extensively to describe this process, particularly in industrialised nations. During this transition, infant and child mortality rates decrease and longevity rises, communicable diseases are controlled and eradicated, and non-communicable and degenerative diseases emerge.

Most high-income or industrialised countries completed the first two stages of epidemiological transition decades ago. Stage one, the 'age of pestilence and famine', is characterised by high fluctuating mortality rates, a low life expectancy at birth, and epidemics, famine and war as the main causes of death. This is followed by stage two, the 'age of receding pandemics', when mortality starts to decrease and is accompanied by a marked increase in life expectancy, although high levels of communicable disease remain.[6] By controlling infectious diseases, reducing malnutrition and improving healthcare (including maternal) services, industrialised countries moved into stage three, the 'age of degenerative and man-made diseases'.[1,6] Deaths from CDs remain invisible during this process of transition – 'buried' among deaths caused by communicable diseases – to emerge only as the latter are adequately controlled. CDs then become proportionately more significant in overall neonatal, infant and child mortality.

CDs attained public health significance in industrialised nations as they moved into the third stage of epidemiological transition in the early 1960s.[1] Since 85 - 90% of CDs have a genetic cause, their birth prevalence and resulting mortality remained high,[1] causing them to emerge and persist as a leading cause of child death in industrialised nations. A comparative study of death rates in England and Wales for 1901 and 1971 demonstrates this: a 68% reduction in non-communicable diseases occurred between 1901 and 1971, but the number of deaths caused by CDs remained unchanged.[1]

Epidemiological transition and CDs in SA

SA, like many LMICs, has not followed the classic model of epidemiological transition experienced by industrialised nations, as a result of the HIV/AIDS and TB epidemics.[7] Fig. 1 plots the under-5 mortality rate (U5MR), infant mortality rate (IMR) and life expectancy at birth (longevity) data for SA over the past 25 years. From 1960, a clear trend of decreasing infant and under-5 mortality and increasing longevity continued until 1992, when life expectancy at birth peaked at 62.33 years. In 1993, both the U5MR and the IMR were at an all-time low of 58.2/1 000 live births and 45.1/1 000 live births, respectively. At this point it appeared as if SA would follow the three classic stages of epidemiological transition, approaching the early phases of transition from stage two of the 'age of receding pandemics' to stage three, the 'age of degenerative and man-made diseases'.[6]

As a result of this falling childhood mortality in the early 1990s, CDs began to emerge as a public health issue. The *Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities* were published by the NDoH in 2001.[8] These outlined goals, objectives, strategies and delivery of clinical and laboratory services appropriate for the care and prevention of CDs. In 2004, the *National Guidelines for the Care and Prevention of the Most Common Genetic Disorders, Birth Defects and Disabilities*[9]

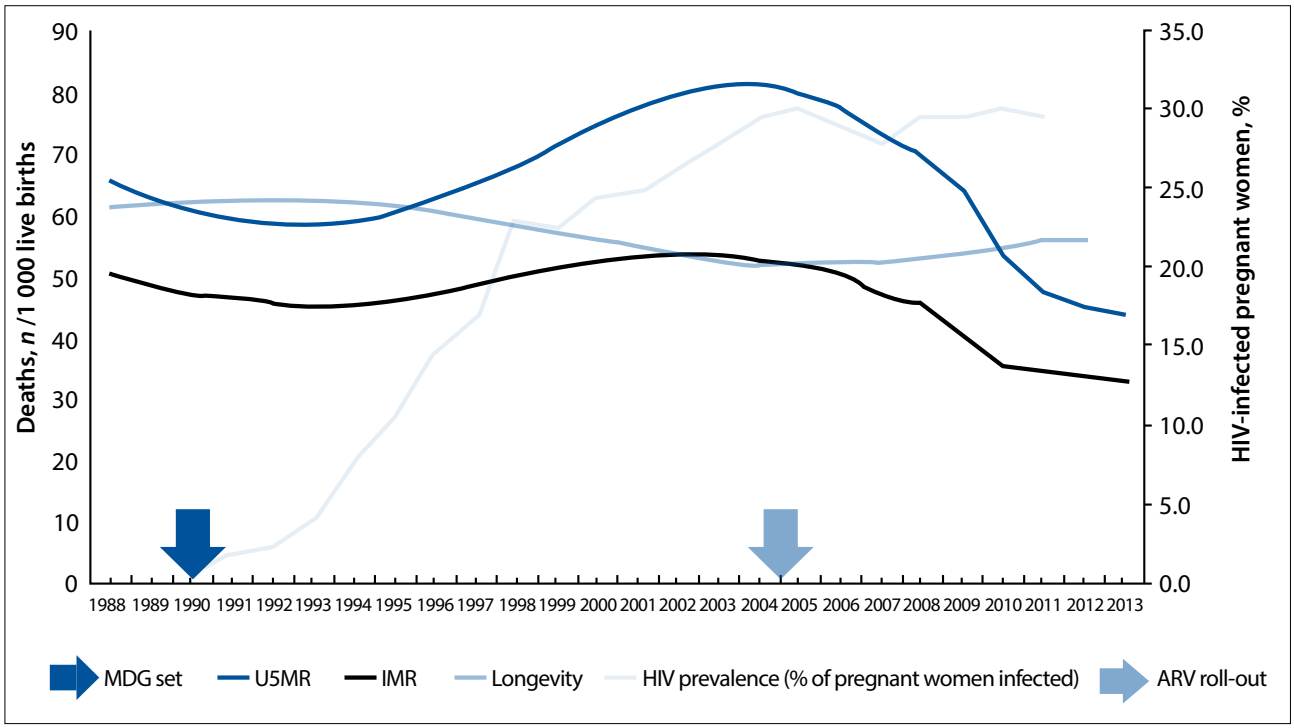

Fig. 1. Epidemiological transition in SA over the past 25 years, as demonstrated by data for childhood mortality,[18] longevity[19] and the HIV epidemic.[20]

were published, targeting primary healthcare providers, describing common CDs and strategies for their care and prevention. However, progress in epidemiological transition was dramatically interrupted and reversed in the mid-1990s with the advent of the concomitant HIV/AIDS and TB epidemics (Fig. 1). Over a 10-year period, HIV prevalence in pregnant women soared from 7.6% in 1994 to 29.5% in 2004. Child mortality rose dramatically, with the U5MR peaking at 80.8/1 000 live births in 2003 and the IMR at 53.2/1 000 in 2002. Life expectancy dropped to 51.56 years in 2005, an all-time low since the 1960s. SA was no longer following the sequential stages of transition as HIV/AIDS caused the resurgence of TB, adding a stage to Omran's concept known as the 'age of emergent and re-emergent infections'.[7,10,11] Combined with the simultaneously increasing burden of non-communicable diseases in the population, this has led to a 'double burden of disease'.[11]

In 2004, the prevalence of HIV infection among pregnant women plateaued at 30% and the U5MR started to reduce as a result of scaled-up prevention of mother-to-child transmission and expanded roll-out of antiretroviral (ARV) therapy.[12] The 2002 IMR of 53.2/1 000 live births dropped to 33.5 in 2012 (Fig. 1). This is lower than the all-time best IMR of 45/1 000 live births in 1993 prior to the HIV/AIDS epidemic. However, since 2011 both the IMR and U5MR have stagnated without significant further reductions.[13]

A major effect of the HIV/AIDS and TB epidemics was to 'bury' the issue of CDs. As services for HIV/AIDS developed, funding and attention were diverted away from tertiary medical genetic services. If child mortality, including neonatal deaths, is to decrease further, control of these ongoing epidemics cannot be at the expense of other child healthcare needs.[12]

Services for the care and prevention of CDs in SA are now at a lower base than in 2001. The 2003 recommendations for human capacity requirements to be trained and in-post by 2010 to meet the expected, and now increased, health needs remain unfulfilled.[14] Personnel levels are similar to, or lower than, those in 2001, with 11 medical geneticists today compared with four in 2001 and the 20 recommended by 2010.[14] Of the nine genetic counsellors in posts today, only four are in the state system (T Wessels, personal communication, 2014), compared with approximately 20 in 2001, and the 80 recommended.[14] Budget cuts have compromised medical genetic diagnostic laboratory services countrywide.

In 2013, SA was reported as the only country of eight emerging economies evaluated where positive development in improving medical genetic service structures had ceased and indeed regressed.[3] This decline will take time to reverse, and the dire state of these services, including the lack of policy addressing childhood disability, must be recognised by those in authority and urgently rectified.

Conclusion

While SA has missed attaining MDG4, it has significantly reduced the U5MR and IMR under difficult circumstances. The previous negative epidemiological transition, premised on the HIV/AIDS epidemic, has reversed and is once again positive with an IMR of 33/1 000 live births.[7] SA must now confront the issue of developing services for the care and prevention of CDs to reduce the stagnating child mortality rates.[13] The current IMR is now below 40/1 000 live births, at which point countries recognise the coming health needs of CDs and strive to implement appropriate services.[15] The proportion of deaths from CDs in SA under-5s was 4% in 2008,[3] and may be expected to rise as childhood deaths from CDs increasingly emerge as a leading cause of death in children while deaths from infections, particularly HIV/AIDS, decrease.

Legislation entitles those affected and living with CDs, including those disabled as a result, to the 'best possible patient care' in the prevailing circumstances, and provides for access to prevention by appropriate interventions.[16] With the global focus, including that of SA, shifting to non-communicable diseases, CDs must be contextualised as the first non-communicable disease experienced by people. CDs deserve to be prioritised, in accordance with WHA Resolution WHA63.17, to ensure the human dignity and constitutionally and legally enshrined human rights of those affected and their families.[2,17]

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S Afr Med J 2015;105(3):186-188. DOI:10.7196/SAMJ.9136

Post-Script to Chapter 3

Following publication of this paper the PhD examiners identified specific edits that would further improve the quality of the paper. While we acknowledge that the version of the paper published by the journal will remain unchanged we would like to specify the following amendments:

- Page 39, column 2, paragraph 1, line 9, amendment: 'In 1993, both the U5MR and IMR were at the ***lowest point to date*** of 58.2/1 000 live births and 45.1/1 000 live births respectively.' It was incorrect to say at an '***all-time low'*** since both the U5MR and IMR have dropped below these figures since then, as detailed on page 40, column 1, paragraph 6.
- Page 40, column 1, paragraph 2, line 5-6, amendment: 'This is lower than the ***previously lowest recorded*** IMR of 45/1 000 live births in 1993 prior to the HIV/AIDs epidemic.' It was incorrect to say an '***all-time best IMR'*** since the IMR has since dropped to below 40/1 000 live births, see column 1, paragraph 6, line 5.

Chapter 4: Constitutional, legal and regulatory imperatives for the renewed care and prevention of congenital disorders in South Africa

This article was published in the South African Journal of Bioethics and Law.

Malherbe HL, Christianson AL, Aldous C, Christianson M. Constitutional, legal and regulatory imperatives for the renewed care and prevention of congenital disorders in South Africa. S Afr J BL. 2016;9(1 MAY):11-7. doi:7196/SAJBL.429.

Constitutional, legal and regulatory imperatives for the renewed care and prevention of congenital disorders in South Africa

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Medical genetic services for the care and prevention of congenital disorders have declined significantly in recent years due to competing health priorities, with previously developed services becoming compromised. With an infant mortality rate of 28/1 000 live births, South Africa (SA) has passed the threshold of 40/1 000 when such services should be implemented. This article outlines the international background and SA legislative framework for medical genetic services and their implementation**.** International, regional and national conventions, legislation, and policy were studied for relevance to genetic services and their implementation was evaluated, including a comparison of sector capacity between 2001 and 2015**.** A comprehensive legislative and regulatory framework exists in SA for the provision of medical genetic services, but implementation has been fragmented and unsustained. Congenital disorders and genetic services are not prominent in national strategies and excluded from interventions aimed at combating child mortality and non-communicable diseases. Capacity today is at a lower level than in 2001. The failure to recognise the burden of disease represented by congenital disorders is the underlying reason for the implementation and service shortfall. Child mortality rates have stagnated since 2011 and can be significantly further reduced by prioritising healthcare issues other than HIV/AIDS, including congenital disorders. It is now an imperative that SA responds to World Health Assembly Resolution 63.17 and prioritises congenital disorders as a healthcare issue, providing services to uphold the dignity and human rights of the most vulnerable members of society.

S Afr J BL 2016;9(1):11-17.DOI:7196/SAJBL.429

Congenital disorders (CDs) are an underestimated critical health issue. Competing health priorities have resulted in the neglect of medical genetic services for the care and prevention of CDs. While a comprehensive national legislative and regulatory framework exists for these services, providing for the fundamental and socio-economic rights enshrined in the constitution, poor implementation has resulted in shortfalls in service for those affected by CDs, many of whom are living with disability.

The internationally agreed definition of CDs are abnormalities of structure or function present from birth, which may be evident at birth or manifest later in life.[1] Although CDs are a global problem, over 90% occur in middle- and low-income countries (MLIC), where 95% of those affected consequently die.[2] In South Africa (SA), one in every 15 live births is affected by a CD.[3] Modelled data indicate a minimum of 6.8% of SA births, of which 80.5% are caused by genetic factors and 19.5% by teratogens.[2,3] CDs are often undiagnosed, or misdiagnosed due to a lack of awareness of attending clinicians to make appropriate diagnoses.[2,4,5] Mortalities as a result of CDs are often incorrectly attributed, burying CDs as an issue.[2,4,5] However, up to 70% of CDs can be prevented, cured or the resulting disability ameliorated through appropriate, timely treatment.[2,6] Lack of data resulting from poor diagnoses results in the CD burden being under-reported in many MLIC countries, where CDs are substantially under-reported.[3,4,5,7] In SA, only 2 174 CD cases were documented in 2012 via the Birth Defect Collection Tool administered by the Department of Health,[8] compared with the

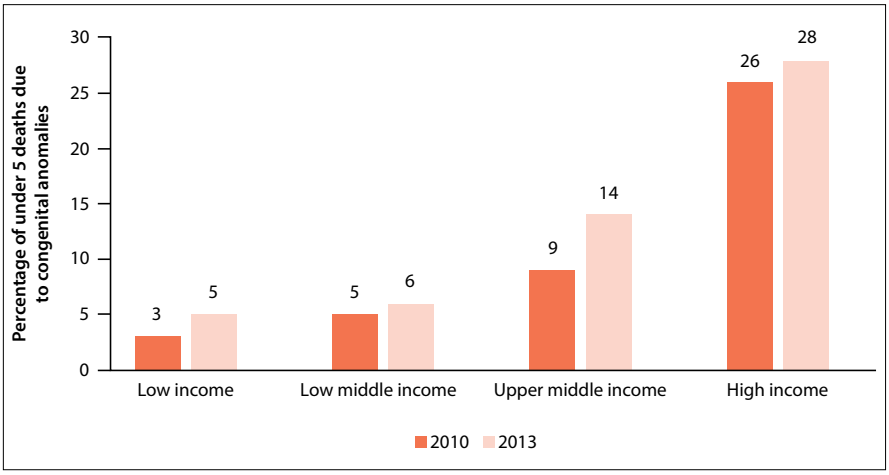

Fig. 1. Comparison of the percentage of under-five deaths resulting from congenital anomalies for World Bank Country Classifications.[9]

83 118 (6.8%) expected, indicating under-reporting of 97%.[3,9]

As SA develops, the proportion of childhood deaths from CDs is increasing, as mortality from communicable diseases decreases.[3,9] This follows the epidemiological trend in industrialised countries where CDs emerged and remain as the leading cause of child death and disability.[2,3] Fig. 1 compares the percentage of under-five deaths resulting from congenital anomalies (a subset of CDs) between the World Bank Country Classifications according to Gross National Income (GNI) per capita.[9] The proportion of deaths from congenital anomalies in all GNI groups increased between 2010 and 2013, and in high-income countries they are the leading cause of deaths, accounting for 28% in children under five.

Significant reductions in the infant mortality rate (IMR) and the under-five mortality rate (U5MR) were seen between 2008 and 2011 from comprehensive HIV/AIDS interventions and the childhood Expanded Programme of Immunisation.[10,11] However, both the IMR and the U5MR have stagnated since 2011 and the neonatal mortality rate since 2009.[12] This indicates that health issues other than those being addressed, such as CDs, require prioritisation.[3,9,10,12] In 2013, congenital abnormalities (obvious structural abnormalities) overtook infection as the third leading cause of death in early neonates, accounting for 11.24% of early neonatal deaths in infants weighing >1 000 g compared with 8.84% from infection.[13] When the IMR falls below 20/1 000 live births in a country, CDs emerge as the leading cause of infant death.[14]

Fig. 2 illustrates the IMR decreasing as countries develop and transition epidemiologically, and the increasing proportion of CD-related infant deaths.[9] The need for medical genetic services is usually recognised by nations when their IMR falls below 40/1 000 live births, as infant and child mortality can be significantly further reduced through such measures.[4,5,14,15] Up to 40% of serious congenital malformations which may be fatal if untreated, can be cured by surgical intervention, and in 30% of cases the degree of resulting disability can be reduced through relevant treatment.[4,6] With an IMR of 28 live births in 2014[12] SA is beyond the point when appropriate services should be implemented to further reduce child mortality and to better care for those who are disabled by CDs.[3,4,9,14,15,]

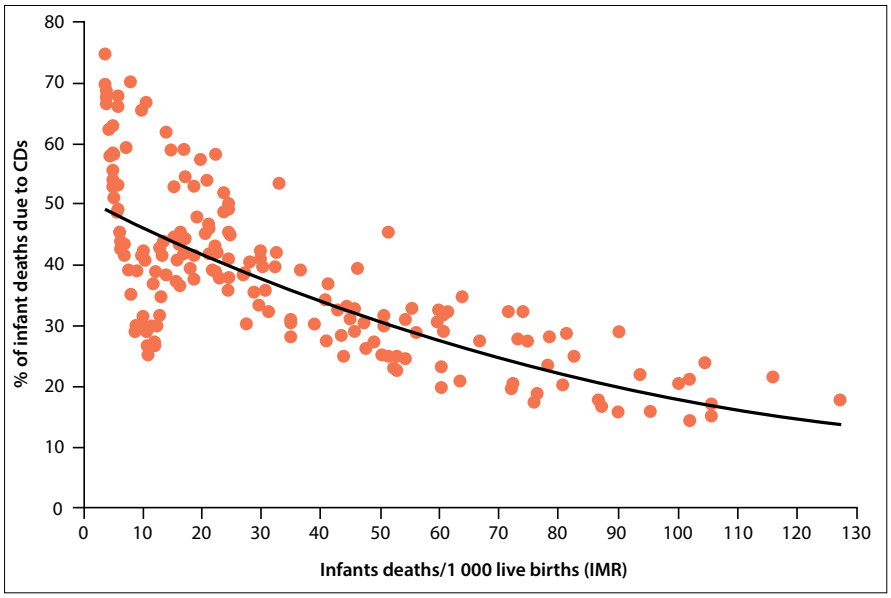

Fig. 2. Relationship between infant mortality and percentage of infants dying from CDs, based on global country figures.[9]

Medical genetic services for the care and prevention of CDs ensure that people with CDs, or at reproductive risk of having children with CDs, can live and reproduce as normally as possible.[5,16] They are key in reducing the contribution of CDs to the disease burden and should provide the 'best possible patient care' in the prevailing circumstances for those affected or at risk of CDs.[9,15,16] Medical genetic services established at human genetics departments and medical schools have been the mainstay in SA since the 1970s.[9] Access to these services has been limited to urban areas with some rural outreach.[9]

Services began to improve in the late 1990s and early 2000s, when CDs first emerged as a health issue and the Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities were published.[17] However, service implementation continued through the established framework of academic centres, rather than integrating services into primary healthcare and extending clinical genetic services beyond urban areas, as was recommended in the 2001 Policy Guidelines.[9,17]

Constitutional, legal and regulatory framework in SA

Several international treaties and resolutions indicating global political commitment towards CDs are applicable to SA and summarised in Table 1. Notable is World Health Assembly (WHA) Resolution 63.17 of 2010.[18] This recognises the importance of CDs as a cause of stillbirths and neonatal deaths, and their contribution to the U5MR and attaining Millennium Development Goal (MDG) 4 to reduce child mortality by two-thirds.[19] Achieving MDG4 required 'accelerated progress in reducing neonatal mortality including the prevention and management of birth defects.[9,18] Although progress was made towards an U5MR of 20/1 000 live births, MDG4 was not achieved.[9]

SA is a signatory to international protocols and conventions that have resulted in national legislation (Table 1).[9] Most relevant to medical genetic services is the United Nations Convention on the Rights of Persons with Disabilities (UNCRPD).[20] Signed and ratified in 2007, the UNCRPD promotes, protects and ensures full and equal enjoyment of all human rights and fundamental freedoms by all persons with disabilities and promotes respect for their inherent dignity.[20] The United Nations Convention on the Rights of the Child (UNCRC), ratified by SA in 1995, concerns the rights of the disabled child without discrimination, while ensuring dignity, promoting self-reliance and community participation.[21]

The Constitution and National Legislation

A comprehensive, national legislative framework exists in SA for the provision of medical genetic services (Table 2).[9] The constitution of SA underpins all other

legislation and provides for fundamental rights to equality, dignity, freedom and security of the person, education and life.[22] Section 27 provides for the socio-economic right of everyone to access healthcare services, including reproductive healthcare, and social security: women, children and people with disabilities are entitled to these s27 rights with the qualification that:

'[t]he State must take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of each of these rights'.[22]

Children's rights not subject to the concept of progressive realisation are listed in s28(1)(c), which states that every child has the right:[9]

'to basic nutrition, shelter, basic health care services and social services'.[22]

Table 1. International treaties, conventions, declarations, protocols of relevance to medical genetic services[9]

Document	Article/rule/overview
World Programme of Action Concerning the Disabled (1982)[35]	Prevention, rehabilitation and equalisation of opportunities
Standard Rules on the Equalisation of Opportunities for Persons with Disabilities (1993)[36]	Rules: 1. Awareness raising; 2. Medical care; 3. Rehabilitation; 4. Support service; 5. Accessibility
United Nations Convention on the Rights of the Child (signed 1993 and ratified 1995)[21]	Articles: 2. No discrimination; 6. Right to life; 23. Disabled child; 24. Healthcare; 26. Social Security
International Covenant on Economic, Social and Cultural Rights (1966) (signed 1994 and ratified 2015)[37]	Article: 12. Physical and mental health
United Nations Millennium Declaration (signed 2000)[19]	Goal 4: Reducing under-five mortality by two-thirds by 2015
United Nations Convention on the Rights of Persons with Disabilities (signed and ratified 2007)[20]	Articles: 5. Equality/non-discrimination; 6. Women with disabilities; 7. Children with disabilities; 8. Awareness raising; 9. Accessibility; 10. Right to life; 19. Living independently; 20. Personal mobility; 23. Respect for home and family; 25. Health; 26. Habilitation and Rehabilitation
African Charter on the Rights and Welfare of the Child ('Children's Charter') (signed 1997 and ratified 2000)[38]	Articles: 5: Right to life;13. Protection of physically/mentally disabled to ensure dignity; 14. Physical/mental health and healthcare
The New Partnership for Africa's Development (2001)[39]	Healthcare provision and delivery
African Youth Charter (signed and ratified 2009)[40]	Articles: 16. Health; 23. Girls and young women; 24. Mentally/physically challenged youth
World Health Assembly Resolution 63.17 (signed and ratified 2010)[18]	Urges member states to address CDs as a healthcare issue through specific actions

Table 2. Key national legislation of relevance to medical genetic services[9]

Title	Overview and sections relevant to CDs
Constitution of the Republic of South Africa (108 of 1996)[22]	Chapter 2: Bill of Rights. Sections: 9. Equality; 10. Human dignity; 11. Life; 27(1)(a). Access to healthcare services, including reproductive healthcare; 27(1)(c). Access to social security including appropriate social assistance; 28(1)(c). Every child has the right to basic healthcare services
Health Professions Act (56 of 1974)[28]	Regulates the health professions through the Health Professions Council of South Africa
National Health Act (61 of 2003)[23]	Sections: 4(3)(a). Free healthcare to pregnant/breastfeeding women, children under six not members/beneficiaries of medical aid schemes (c) free termination of pregnancy; 21(2)(b)(vii). Genetic services; 21(2)(k) & 25(2)(w). Management, prevention and control of communicable and NCDs; 23 (1)(a)(ix) & 27(1)(a)(ix). Epidemiological surveillance/ monitoring of national and provincial trends; 21, 23, 25 & 27. Implementation of national/provincial policy and compliance; 39(2)(a)&(d) and 70(2)(d) Health needs of vulnerable groups including children and people with disabilities; 48. Development and provision of human resources in national health system; 52. Regulations relating to human resources; 70. Identification of health research priorities
Choice on Termination of Pregnancy Act (92 of 1996)[24]	Sections: 2(b)(ii) and minors 5(5)(a)(ii) Termination of pregnancy (TOP) between 13 - 20 weeks inclusive if substantial risk that the fetus would suffer from a severe physical/ mental abnormality Sections: 2(c)(ii) and minors 5(5)(b)(ii) TOP after the 20th week if the continued pregnancy would result in a severe malformation of the fetus
The National Health Laboratories Service Act (37 of 2000)[26]	Laboratory services for the public health sector Sections 4 & 5: Cost-effective and efficient health laboratory services including training
Mental Health Care Act (17 of 2002)[25]	A legal framework for mental health in SA with an emphasis on human rights
The Nursing Act (33 of 2005)[27]	Regulates the nursing profession through the South African Nursing Council
Children's Act (38 of 2005)[30]	Sections: 11. Children with disability or chronic illness; 156(1)(g). Care and protection
Social Assistance Act (13 of 2004)[29]	Sections: 7. Care dependency grants; 9. Disability grants

This includes children with CDs, and those living with disability caused by CDs.

National Health Act

The National Health Act (NHA) 61 of 2003 provides a framework for a single healthcare system for the country, rectifying the socio-economic imbalances and inequities of the health services of the past and provides for many of the rights outlined in the Bill of Rights.[23]

The NHA is the only piece of national legislation in which genetic services feature prominently. A clear directive is included in Chapter 3, under Main functions of the National Department in s21(2)(b)(vii):[9]

'the Director-General must, in accordance with national health policy, issue and promote adherence to, norms and standards on health matters including genetic services.'[23]

Genetic services are listed among other vital services, including sterilisation and termination of pregnancy, and the provision of health services/healthcare services for convicted persons and persons awaiting trial, highlighting the considered importance of these services.

The NHA stipulates that the national policy is executed via the provincial departments of health in a top-down approach. National and provincial health councils ensure national policy is implemented provincially and that provincial health plans comply with national policy (NHA s21, 23, 25, 27).[23] To date, no provincial policies or health plans for genetic services have been developed, with the exception of the Western Cape (Prof. Raj Ramesar and Dr Mike Urban, personal communication), and most provinces refer to the 2001 national policy[17]

Other sections of the NHA relevant to medical genetic services include:

- management, prevention and control of non-communicable diseases (NCDs) through healthcare services (s21(2)(k) and s25(2)(w))
- epidemiological surveillance and monitoring of disease trends (s23(1)(a)(ix) and s27(1)(a)(ix))
- identification of priority health problems and research priorities relevant to the burden of disease (s70)
- health needs of vulnerable groups, including children and people with disabilities (s39(2)(a)&(d), s70(2)(d))

Table 3. National policies, strategies, guidelines, charters and initiatives relevant to medical genetic services

Document	Year	Overview
Integrated National Disability Strategy White Paper[41]	1997	The right of people with disabilities to play a full, participatory role in society
Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities[17]	2001	Goals, objectives, strategies and delivery of clinical and laboratory services for the care and prevention of CDs, including human capacity recommendations
Guidelines on Ethics for Medical Research. Book 2. Reproductive Biology and Genetic Research[42]	2002	Section 3.3: Genetic screening and testing
Department of Health. Strategic Framework for the Modernisation of Tertiary Hospital Services[43]	2003	Human genetics throughout document in proposed models. Appendix 4: Revised human capacity recommendations
National Guidelines for the Care and Prevention of the Most Common Genetic Disorders, Birth Defects and Disabilities[31]	2005	Targeting primary health care providers, describing common CDs and strategies for their care/prevention
National Perinatal and Neonatal Morbidity and Mortality Committee[45]	2008	Audit perinatal and neonatal deaths and produce annual reports and final report in 2011
National Patients' Rights Charter[46]	2008	Common standard to realise, uphold, promote and protect the constitutional right of access to healthcare services Section 2: Access to healthcare; 2(3)(c) Provision for special needs (newborn, children, pregnant women, disabled); (d) Counselling; (e) Palliative care; (g) Health information
Negotiated Service Delivery Agreement. Outcome 2: A long and healthy life for all South Africans[47]	2010	Strategic outputs: 1. Increasing life expectancy, NCDs and burden of disease; 2. Decreasing maternal and child mortality; 4. Strengthening health system effectiveness
National Health Insurance in South Africa Policy Paper[48]	2011	To transform existing institutions/organisation in the healthcare system to make the system more equitable, offering universal coverage to a defined comprehensive package of services
South Africa's National Strategic Plan for a Campaign on Accelerated Reduction of Maternal and Child Mortality in Africa[49]	2012	To rapidly reduce maternal and child mortality
Strategic Plan for Maternal, Newborn, Child and Women's Health and Nutrition in South Africa 2012-2016[33]	2012	Reducing maternal and child mortality. Long-term health conditions in children (p24)
Committee on Morbidity and Mortality in Children Under 5 Years[50]	2012	Reviews and monitors maternal, perinatal and childhood mortality and morbidity data in SA
National Department of Health: Strategic Plan 2014/15-2018/19[32]	2014	Programme 3: Maternal and child health. NCDs
Guidelines for Maternity Care in South Africa[44]	2015	Chapters: 4. Antenatal care; 9. Pregnancy problems; 10. Intrauterine, neonatal deaths and stillbirths; 15. Screening for congenital anomalies

- human resources including adequate resources for education and training of healthcare personnel (Chapter 7).[23]

Other national legislation

Other key national legislation provides for different aspects of genetic services and are summarised in Table 2.[9] Notable are:

- The Choice on Termination of Pregnancy Act (1996), used as part of a preventive strategy when severe abnormalities are detected *in utero* (s2(b)(ii), 2(c)(ii), s5(5)(a)(ii), s5(5)(b)(ii).[24]
- The Mental Health Act (2002) provides a legal framework for mental health, emphasising the human rights of the mentally ill.[25]
- The National Health Laboratories Service (NHLS) Act (2000) provides for laboratory services as an essential component of genetic services.[26]
- The Nursing Act and the Health Professions Act provide for statutory bodies regulating these professions.[27,28] In SA, genetic counsellors require registration under the Health Professional Council of South Africa.[28]
- Social Assistance Act (2004) provides for care dependency and disability grants.[29]
- Matters concerning the disabled child are specified in the Children's Act (2005).[30]

National policy

Two key policy documents focus solely on CDs: National Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities[17] and National Guidelines for the Care and Prevention of the Most Common Genetic Disorders, Birth Defects and Disabilities.[31] The National Policy Guidelines outline goals, objectives, strategies, personnel requirements and delivery of clinical and laboratory services appropriate for the care and prevention of CDs.

Despite these policies, CDs are not regarded as a healthcare issue in SA strategic plans (Table 3), despite the emphasis on reducing child mortality in response to MDG4. The Department of Health (DoH) Strategic Plan 2014/15-2018/19 recognises mental health disorders as a NCD, aiming to improve access to services through screening and treatment, but does not acknowledge the significant genetic component of many of these disorders.[32]

In the DoH Strategic Plan for Maternal, Newborn, Child and Women's Health and Nutrition in South Africa 2012 - 2016, CDs are mentioned as a cause of neonatal death, contributing to 15 - 20% of children affected by a long-term/chronic health conditions who are 'not receiving the care they require'.[9,33] No responding interventions are outlined.[9] NCDs are a key strategic focus in these policies, but there is no cognisance that CDs are an NCD, the first experienced in life, contributing to the 43% of NCD related deaths annually in SA.[14,34]

A draft Disability Rights Policy, a first step to implementing the UNCRPD[20] was published for public comment in early 2015. A review of several health and disability policy documents is underway, including the 2001 Policy Guidelines [17] and accompanying clinical guidelines proposed.

Implementation

Despite the existence of a comprehensive legislative framework for the development of medical genetic services, implementation has fallen short and medical genetic services are in decline.

In Table 4, personnel capacity is compared between 2001 and 2015, demonstrating that these services are at a lower base today than in 2001.[3,9]

Of over 1 000 healthcare providers, mainly labour ward nurses, trained through the Medical Genetics Education Programme (MGEP), less than 100 remain in services for care and prevention of CDs.[9] The lack of continued support forced trainees to discontinue their genetic nursing role and move to non-related fields. This has resulted in reduced clinical capacity to identify and diagnose CDs and has influenced the surveillance of CDs.[9]

SA is the only country (of eight emerging economies) where positive development in improving medical genetic service structures has ceased and indeed regressed.[3,7]

Reasons for this decline since 2001 include competing health priorities that have redirected political commitment and funding.[3,9] The lack of investment in medical genetic services has resulted in insufficiently trained personnel, inadequate capacity at all levels, and severely compromised laboratory services.[3,9] These shortfalls make it impossible to uphold the constitutional rights of those affected by CDs, including children and those living with disability, through the practical provision of the services they require.

Conclusion

While the SA constitution is admired globally for its protection of human rights, there has been a failure to translate these constitutional imperatives into effective, accessible services for the care and prevention of CDs. Failure to recognise the burden of disease represented

Table 4. A comparison of medical genetic services capacity in 2001 and 2015[9]

	Recommended*	2001‡		2015	
Category	**Number/ratio (Pop = 46 13 m)†**	**Number ‡**	**Ratio (Pop = 44 82 m)†**	**Number**	**Ratio (Pop = 54 96 m)§**
Medical geneticists	20/1 per 2 m	4	1 per 11.2 m	12¶	1 per 4.6 m
Genetic counsellors	80/1 per 580 000	<20	1 per 2.2 m	9∏	1 per 6.1 m
Medical scientists/ technologists	100/1 per 450 000	50	1 per 900 000	26**	1 per 2.1 m

* Department of Health. Strategic Framework for the Modernisation of Tertiary Hospital Services. Discussion Document. Pretoria, South Africa: Department of Health, 2003;86.
‡ Department of Health. Policy Guidelines for the management and prevention of genetic disorders, birth defects and disabilities. Pretoria, South Africa: Department of Health, 2001.
† Statistics South Africa. South African Statistics 2014. Pretoria, South Africa: Statistics South Africa, 2014.
§ Statistics South Africa. Mid-Year Population Estimates 2015. Pretoria, South Africa: Statistics South Africa, 2015.
¶ No medical geneticists are employed by the State in Gauteng. Personal communication: A. Krause, 11 February 2016.
∏ Figure increased to 9 in April 2016 plus 6 in private practice. Personal communication: T. Wessels, 25 February 2016.
** NHLS academic medical scientists only. Personal communication: H. Soodyall, 27 July 2015.

by CDs is the underlying cause of this unethical shortfall in services.[9] Despite the comprehensive legal framework remaining unchanged, the implementation of this legislation has declined. 'We have the constitution, the law, the guidelines and policy – but good laws are being lost in translation' (Prof. Marylyn Christianson, Special Olympics Disability Summit, Shanghai, 2007). In the words of the 2013 GenTee Report,[7] 'the continuing lack of commitment to the country's constitutional, legal and regulatory framework [has resulted in] an implosion of genetic services in the public domain due to very limited public will, commitment and funding [resulting in] inequitable genetic services [impacting] the ability of the poorer population to utilize services according to their needs'.

It is an imperative that SA responds to WHA 63.17[18] and prioritises CDs as a healthcare issue by providing the required medical genetic services to uphold the dignity and human rights of people with CDs, the most vulnerable of our society.

Acknowledgement. This research was undertaken with the assistance of a bursary from the College of Health Sciences, University of KwaZulu-Natal.

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Post-Script to Chapter 4

Following publication of this paper the PhD examiners identified specific edits that would further improve the quality of the paper. While we acknowledge that the version of the paper published by the journal will remain unchanged we would like to specify the following amendments:

- Page 43, column 1, paragraph 4, line 16, amendement: 'With an IMR of **28/1 000** live births in 2014…' The '**/1 000'** was excluded in the published text and may be misleading.

Chapter 5: Review of the 2015 Guidelines for Maternity Care with relevance to congenital disorders

This article was published in the South African Medical Journal.

Malherbe HL, Woods DL, Aldous C, Christianson AL. Review of the 2015 Guidelines for Maternity Care with relevance to congenital disorders. S Afr Med J. 2016;106(7):699-71. doi:10.7196/SAMJ.2016.v106i8.11129.

ISSUES IN PUBLIC HEALTH

Review of the 2015 *Guidelines for Maternity Care* with relevance to congenital disorders

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The 4th edition of the *Guidelines for Maternal Care in South Africa* published by the National Department of Health in 2015 was evaluated with relevance to the care and prevention of congenital disorders (CDs). Disparate terminology is used for CDs throughout the guidelines, and overall less detail is included on CDs compared with the previous edition. This demonstrates a lack of awareness around the growing health need and contribution of CDs to the disease burden in South Africa (SA). Referrals to medical genetic services in the guidelines for mothers of advanced maternal age and other high-risk categories do not take into account the insufficient capacity available for screening and diagnosis of CDs. This highlights the lack of consultation with the medical genetics sector during the development of the guidelines. To respond to the Sustainable Development Goals by 2030, CDs must be integrated comprehensively at all levels of healthcare in SA.

S Afr Med J 2016;106(7):669-671. DOI:10.7196/SAMJ.2016.v106i7.10813

In 2015, the 4th edition of the *Guidelines for Maternity Care in South Africa* was published by the National Department of Health (NDoH).[1] A manual for clinics, community health centres and district hospitals, these replaced the previous 2007 edition.[2]

The guidelines provide, among other things, a practical approach for primary healthcare to manage pregnancy, labour and delivery in South Africa (SA) with the ultimate aim of reducing maternal mortality (deaths during pregnancy or within 42 days of delivery). With the maternal mortality ratio (MMR) estimated as having quadrupled in SA due to the HIV/AIDS epidemic, the need for such guidelines is clear.[3] At 154 maternal deaths per 100 000 live births in 2011 - 2013, the MMR was reduced to almost pre-HIV epidemic levels, but the Millennium Development Goal target of 38/100 000 live births was not achieved.[4,5] Sights are now set on the Sustainable Development Goal of a global MMR of less than 70/100 000 by 2030.[6]

Owing to the inextricable link between mother and child, poor maternal health and maternal death are more likely to lead to death of the newborn.[7] With 40% of under-5 deaths occurring during the neonatal period in SA, and 75% of these occurring as early neonatal deaths, the benefits of quality prenatal care for the child are obvious.[8] In SA, deaths in infants and children under-5 decreased rapidly between 2008 and 2011, with a more modest improvement in neonatal deaths from 2009 to 2011, after which all these rates stagnated.[9] Efforts to combat communicable diseases – including HIV/AIDS – continue, and interventions are underway such as those identified in the report by Chola *et al.*,[10] the childhood Expanded Program of Immunization, and improving social determinants of health; these will contribute to further reducing childhood deaths. However, for significant further reductions in childhood mortality and morbidity, including neonatal deaths, the contribution of congenital disorders (CDs) must be addressed.[11,12]

The growing burden of congenital disorders

Data from the Perinatal Problem Identification Program (PPIP) in 2014 indicated that congenital abnormalities have overtaken infection as the third leading cause of early neonatal deaths, after hypoxia and immaturity.[12,13] Since congenital abnormalities (obvious structural CDs identified at birth) are a sub-group of CDs, the true death toll from CDs is likely to be much higher. CDs, which are abnormalities of structure or function present from birth – although they may only manifest later in life[14] – are estimated to affect one in 15 live births in SA.[11] CDs have not been prioritised as a healthcare issue in SA, despite World Health Assembly Resolution 63.17 of 2010 recognising their contribution to neonatal deaths and calling member states to action.[11,15] The lack of accurate, empirical data has led to an underestimate of the true contribution of CDs to the burden of disease.[16,17]

The purpose of this article is to evaluate the 2015 *Guidelines on Maternity Care* with relevance to the care and prevention of CDs.[1] Where appropriate, these will be compared with the previous edition of the guidelines within the current epidemiological context in SA.[1,2]

What is the aim of the *Guidelines for Maternity Care*?

Prepared by the National Maternity Guidelines Committee at the NDoH, the guidelines are for health workers (doctors and midwives) providing obstetric, surgical and anaesthetic services for pregnant women in primary healthcare facilities where specialist care is not normally available.[1] Clinics, community health centres and district hospitals are encouraged to use the guidelines to develop protocols tailored to their specific needs, for identifying, diagnosing and managing common and serious pregnancy and delivery problems. Both editions of the guidelines respond to report recommendations by the National Committee on the Confidential Enquiry into Maternal Deaths, with the overall aim to improve clinical management and referral to reduce pregnancy-related deaths and ill health.[5]

While the 2015 guidelines follow a similar format to that of the previous edition, they also include some new chapters and omit others.[1,2] Content of relevance to CDs is included in chapters 2: Levels of care; 4: Antenatal care; 9: Problems in pregnancy; 10: Management of intra-uterine deaths, stillborn babies and neonatal

deaths; and 15: Basic ultrasound at district level and routine postnatal care. Additional chapters in the 2015 edition do not include new content relevant to CDs; rather, the level of detail and quality of information on CDs has been decreased.

Confusion in terminology

The most notable difference in the 2015 edition is the use of 14 different terms to refer to CDs, whereas the 2007 edition consistently used the term 'birth defects and genetic disorders'.[2] The internationally agreed term 'congenital disorders' itself is not used in the document, although the synonym 'birth defects' is used several times.[14] Unsupported by a glossary, the terms used include: congenital anomalies; congenital abnormality; congenital infection; chromosomal and congenital defect; abnormalities; structural and chromosomal fetal anomalies; birth defect; genetic or chromosomal defects; genetic disorder; genetic anomalies; genetic disease; familial and genetic disorder; fetal abnormalities; and fetal anomaly. Except for birth defects, these all refer to sub-sets of CDs, and some categories of CDs are excluded (personal communication, Bernadette Modell, November 2015).[14] This inconsistent use of disparate terms for CDs is of concern and causes confusion around this healthcare issue.

Teratogens

In the 2015 edition, teratogens including alcohol, recreational drug use, maternal infections (rubella and syphilis), and the use of teratogenic medications during pregnancy are listed under 'risks for genetic disease'. The risks associated with poorly controlled medical conditions are also listed, but diabetes mellitus is addressed elsewhere in the guidelines and hypothyroidism and iodine deficiency are not mentioned. With teratogens accounting for almost 20% of CDs in SA and affecting 14 000 births annually, these need to be contextualised correctly, with greater emphasis placed on these preventable CDs.[11]

Surveillance

An exclusion from the 2015 guidelines is the regular compilation of data on the number of babies born with genetic disorders and major birth defects, as specified in the 2007 edition. In contrast, the 2015 edition refers only to the recording of mortalities, and recommends the PPIP format for data collation. This sole focus on deaths omits morbidity and the opportunity to provide vital data into national surveillance of CDs.

Other content relevant to CDs

The majority of content relevant to CDs is included in chapters 4: Antenatal care and 10: Management of intra-uterine deaths, stillborn babies and neonatal deaths. In chapter 4, the importance of history taking for familial and genetic disorders to assess risk factors at the first antenatal visit is emphasised, as is 5 mg of folic acid daily 3 months prior to and throughout pregnancy for the prevention of neural tube defects. A concise section entitled 'Risk of genetic disease' lists categories of women of childbearing age potentially at risk of having a child with a 'birth defect or genetic disorder', but includes non-genetic CDs. It recommends the provision of essential information to all pregnant women on specific topics including the avoidance of alcohol, tobacco and recreational drugs, the use of medication (self-care) and genetic disorders and birth defects relevant to newborn and infant care.

Capacity constraints in medical genetic services

In chapter 10: Management of intra-uterine deaths, stillborn babies and neonatal deaths, genetic counselling and relevant referral should be provided as part of postpartum care when CDs are suspected, prior to another pregnancy in case of reoccurrence. Steps outlined to obtain a diagnosis when a CD is suspected as the cause of death include undertaking a history and a basic external examination. When a diagnosis cannot be made, a postmortem or whole body X-ray/digital photography for referral to a geneticist is recommended. This does not take into account the limited capacity available in SA due to there being only 12 practising medical geneticists, clustered around academic centres in urban areas (Table 1).[12]

Capacity in the medical genetic services sector is further underestimated in chapter 15: Basic ultrasound at the district level. While acknowledging that routine screening for structural and fetal anomalies is 'not yet practical in the public sector', all women of advanced maternal age (specified as over 37 years) are referred to a specialist health facility or a maternal fetal ultrasound unit. This includes referral to a genetics clinic where consenting women should be routinely offered a scan, genetic counselling and invasive testing to rule out Down syndrome. It does not specify that genetic counselling should be undertaken prior to the scan and repeated afterwards in the case of abnormal findings. Women with a previous history or family history of structural, chromosomal or genetic disorders are also referred to specialist hospitals for structural screening and management decision. Analysis of recorded live births in 2013 indicates that 84 260 births (8.5%) were to women over 37 years.[22] As outlined in Table 1, current capacity falls far short of recommended levels, with only 12 practising medical geneticists, fewer than 9 genetic counsellors and compromised laboratory services operating almost entirely from academic medical genetic departments countrywide. This available capacity makes it impossible for this number of referrals of women of advanced maternal age to be implemented. Medical genetic services relating to the care and prevention of CDs are in a state of decline and at a lower base today than prior to the HIV/AIDS epidemic.[11,12]

Genetic counselling

In addition to referring high-risk women to regional and tertiary hospitals, genetic screening and counselling services are specified as a function of district hospitals in chapter 2: Levels of care. A significant contribution to the care of newborns is undertaken by nurses in these low-resourced primary healthcare settings, particularly in rural areas. These nurses, and general medical officers, are in the main not equipped with genetic counselling skills, and the nurses who are trained are in short supply. SA is also experiencing a severe shortage of doctors, with only 60 per 100 000

Table 1. A comparison of medical genetics services capacity in 2001 and 2015[12]

	Recommended (2003)[18]	2001		2015	
Category	*n* (ratio) (*N*=46.13m)[19]	*n*[20]	Ratio (*N*=44.82m)[19]	*n*	Ratio (*N*=54.96m)[21]
Medical geneticists	20 (1 per 2m)	4	1 per 11.2m	12*	1 per 4.6m
Genetic counsellors	80 (1 per 580 000)	<20	1 per 2.2m	9†	1 per 6.1m
Medical scientists/ technologists	100 (1 per 450 000)	50	1 per 900 000	26‡	1 per 2.1m

*No medical geneticists are employed by the state in Gauteng. Personal communication, A Krause, 11 February 2016.
†This figure increased to 9 in April 2016, plus 6 in private practice. Personal communication, T Wessels, 25 February 2016.
‡NHLS academic medical scientists only. Personal communication, H Soodyall, 27 July 2015.

population in 2013 compared with the global average of 152/100 000, and even fewer specialists (including medical geneticists).[23] This places a huge strain upon the system and medical practitioners are overworked and often unsupported. This general lack of capacity of healthcare professionals at all levels must be rectified before such an under-resourced system can respond to additional demands.

Conclusion

As management guidelines, the 2015 edition responds to the policy directive to reduce maternal mortality by offering principles from which detailed institutional protocols can be developed. However, the guidelines are not cognisant of the limited infrastructure, capacity and resources available in the medical genetic services sector. The lack of investment in medical genetic services, largely due to competing health priorities, make it impossible for referrals in the guidelines to be implemented.

Consultation with the medical genetics community during the development of the 2015 edition could have prevented this disjoint and would have benefited from the ongoing review of the 2001 *Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities*.[20]

With SA once again in positive epidemiological transition, the proportion of neonatal, infant and child deaths from CDs will continue to increase as the country develops and communicable diseases are better controlled.[11,12] Relevant, accessible and effective medical genetic services can prevent, cure and ameliorate CDs by up to 70% and may be the only way to significantly reduce child mortality further.[11,12,16,17,24] If SA is to respond to Sustainable Development Goal 3 to end preventable deaths in newborns and reduce premature mortality from non-communicable diseases by two-thirds by 2030, CDs must be addressed comprehensively and funding allocated to build capacity and infrastructure in the sector.[6,12] This response must permeate every level of implementation, to ensure no child is left behind.

Acknowledgements. Thanks to Prof. Eckhart Buchmann, National Maternity Guidelines Committee, for his feedback on the article.

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Accepted 4 April 2016.

Part Two: Congenital disorders and child mortality

Moving on from Part one, Part two takes a different approach and contextualizes congenital disorders (CDs) as a contributing factor to child mortality in SA. This is of particular relevance both in SA and internationally due to the Sustainable Development Goals (SDG) (1) set for 2030, particularly the targets for SDG 3. If SA is to meet the goal of reducing the U5MR to 25 per 1 000 live births, several things need to happen. The current 'invisible' burden of CDs needs to be recognized, and the reality that with appropriate care, the burden of CDs can be reduced by up to 70% (2, 3). Although a lot of momentum was gathered as a result of the Millennium Development Goals (MDG) (4), specifically MDG 4 in focusing on reducing child mortality – CDs continue to be overlooked in SA. This chapter highlights that until medical genetic services are implemented – something that usually occurs when the Infant Mortality Rate (IMR) falls below 40-50 deaths per 1 000 live births. SA is yet to implement comprehensive services, despite the IMR reaching 27 in 2015 (5), and will fail to see a significant further reduction in child mortality until it does so. This chapter brings together all the available evidence, building on that provided in Part One. It highlights the need to recognize CDs as a healthcare issue in SA and the urgency to implement medical genetic services if child mortality is to be further significantly reduced.

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Chapter 6: The contribution of congenital disorders to child mortality in South Africa

This chapter was published in the 19th Edition of the South African Health Review.

Malherbe HL, Aldous C, Woods D, Christianson A. The contribution of congenital disorders to child mortality in South Africa. In: Padarath A, King J, Mackie E, Casciola J, editors. South African Health Review 2016. Durban: Health Systems Trust; 2016. p. 137-52.

The contribution of congenital disorders to child mortality in South Africa

12

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Reduction in child mortality has been a priority issue in South Africa leading up to the Millennium Development Goals. However, the contribution of congenital disorders (CDs) to child mortality is yet to be recognised and acted upon.

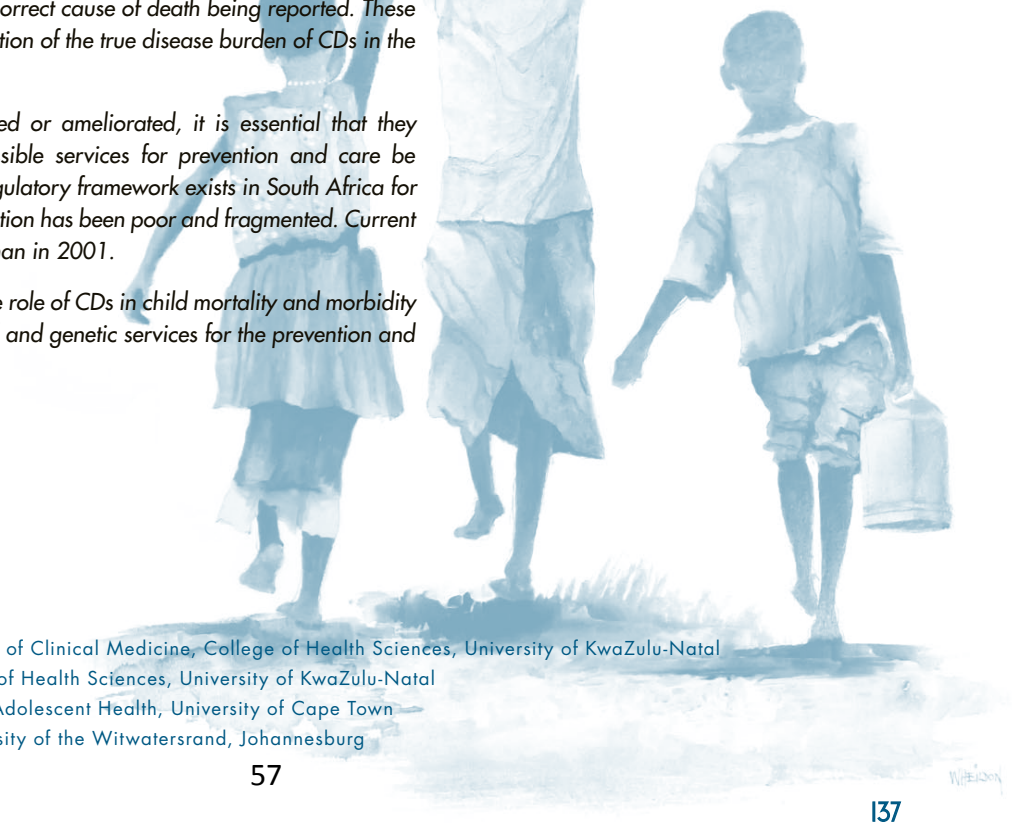
Rapid reductions in child mortality have resulted largely from comprehensive HIV and AIDS programmes and interventions such as the childhood Expanded Programme of Immunisation. However, the Rapid Mortality Surveillance System reports that since 2011, reductions in child mortality rates "stopped abruptly". This indicates that health issues other than those currently being addressed may require long-term prioritisation. In 2013, congenital anomalies (excluding many CDs) overtook infection as the third leading cause of early neonatal deaths, which account for one-third of all under-five deaths.

As South Africa transitions epidemiologically, the proportion of deaths caused by CDs is increasing, as mortality from communicable diseases drops, revealing the previously hidden disease burden of CDs. In South Africa, many CDs go undiagnosed or are misdiagnosed, resulting in the incorrect cause of death being reported. These inaccurate data result in an underestimation of the true disease burden of CDs in the country.

As up to 70% of CDs can be prevented or ameliorated, it is essential that they be prioritised and that relevant, accessible services for prevention and care be implemented. A good legislative and regulatory framework exists in South Africa for the provision of services, but implementation has been poor and fragmented. Current services are available at a lower base than in 2001.

This chapter argues for recognition of the role of CDs in child mortality and morbidity and the potential advantages of medical and genetic services for the prevention and care of CDs.

In South Africa many congenital disorders go undiagnosed or are misdiagnosed resulting in the incorrect cause of death being reported and in an underestimation of the true burden of congenital disorders in the country.



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Introduction

Since the Millennium Development Goals (MDGs) were set in 2000, there has been a global drive to reduce child mortality.[1] In order to achieve the MDG 4 target of cutting under-five mortality by two-thirds by the end of 2015, countries rapidly incorporated measures relevant to their specific healthcare challenges. As the MDG deadline loomed, South Africa focused on responding to the HIV and AIDS and concomitant tuberculosis (TB) epidemics, re-engineering primary health care and developing a strategic plan for Maternal, Newborn, Child and Women's Health (MNCWH) and Nutrition. Several ministerial committees were established to address underlying issues, including the National Perinatal Mortality and Morbidity Committee (NaPeMMCo) and the Committee on Mortality and Morbidity in Children (CoMMiC). The topic of newborn and child mortality and survival has also been examined in detail in previous editions of the *South African Health Review*.[2,3]

None of these policies or initiatives has comprehensively recognised the contribution of congenital disorders (CDs) to neonatal, infant and child mortality and morbidity. This is despite the fact that in industrialised countries around the world, CDs are the leading cause of death in infants and children, contributing up to 28% of under-five deaths in high-income countries.[4] Like many other middle- and low-income countries (MLICs), South Africa is following this epidemiological trend and the proportion of deaths and disability resulting from CDs is rising, especially as communicable diseases are better controlled.[5]

This chapter provides an overview of the health issue of CDs and their unappreciated role in child mortality and morbidity in South Africa. Epidemiological transition is described in relation to CDs and an outline is given of the growing role of CDs in the burden of disease in South Africa and why it has remained hidden. The chapter also identifies the benefits of recognising the contribution of CDs in the burden of disease, including potential reductions in mortality and morbidity through medical genetic services for the prevention and care of CDs. The current status of these services is reviewed and compared with what is required to address this growing health need. Where relevant, secondary data have been sourced from peer-reviewed literature and globally recognised data sources.

Millennium Development Goal 4

The adoption of the United Nations Millennium Development Declaration in 2000[1] and the time-based targets set for the following 15 years has resulted in varying degrees of achievement among participating nations. MDG 4 focused on improving child survival, and significant progress towards this two-thirds reduction in under-five mortality was achieved globally. By 2015, the global under-five mortality rate (U5MR) had been reduced by 53%, halving the number of children dying annually from 12.7 million in 1990 to 5.9 million in 2015.[6] Many regions achieved or came close to the targeted two-thirds (66%) reduction in U5MR. In sub-Saharan Africa, the U5MR decreased by 54%.[6] One in every 12 children still dies before his or her fifth birthday in sub-Saharan Africa compared with one in 147 in high-income countries.[6]

South Africa's progress towards MDG 4 has been varied. In 2005, South Africa was one of only four countries where the U5MR was higher than the 1990 MDG baseline due to the negative epidemiological impact of HIV and AIDS and concomitant TB.[7] Significant reductions were then seen in child mortality until 2011 due to a number of factors. These included scaled-up prevention of mother-to-child transmission of HIV, expanded roll-out of antiretroviral therapy, and the addition of the rotavirus and pneumococcal conjugate vaccines to the childhood Expanded Programme of Immunisation (EPI).[7–9] Despite the rate of reduction tripling since 2000, the U5MR decreased by one-third only, to 39 per1 000 live births,[8] falling short of the South African MDG 4 target of 20 per1 000 live births.

However, according to the Rapid Mortality Surveillance Report there has been no further decrease in infant and child mortality in South Africa since 2011.[8] This stagnation indicates the need to address other health issues contributing to infant and child mortality, whilst continuing with ongoing efforts.[5,7,8] Many issues related to social determinants of health and childhood illnesses are already being addressed, including malnutrition and infectious diseases associated with poverty such as measles, diarrhoea and malaria. A 2013 study identified 15 key interventions that were scaled up in South Africa for maximum impact on maternal and child mortality during the final two years of the MGDs.[10] Preliminary measures to target non-communicable diseases (NCDs), now a component of South Africa's quadruple burden of disease, are also under way.[11] However, CDs, which are the first NCD experienced by infants and children,[5,12] are yet to be recognised for their contribution to stillbirths, and neonatal, infant and child mortality in South Africa. This is despite the global call to action by the World Health Assembly (WHA) in 2010 through Resolution 63.17,[13] which recognised the importance of CDs as a cause of stillbirths and neonatal mortality. To attain MDG 4, WHA 63.17 called for "accelerated progress in reducing neonatal mortality including the prevention and management of CDs".[13]

CDs are a common, costly and critical health issue. According to the 2006 March of Dimes report,[14] serious CDs result in the death of 3.3 million children under the age of five globally every year. Although CDs are found in all populations throughout the world, over 90% occur in MLICs where 95% of CD-related deaths occur.[14] Reasons for this unequal distribution of CDs include less-developed health services and a variety of poverty-related reasons that increase the risk of CDs occurring, such as a higher percentage of older mothers and consanguineous marriages, and the survival advantage against malaria for carriers of some single gene disorders.[14] Despite this higher incidence of CDs in MLICs, the contribution of CDs to the burden of disease is yet to be recognised by many of these countries.

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".[15] CDs that are caused before conception are genetic and the result of chromosomal abnormalities or single gene defects, or are multifactorial in origin. Post-conception CDs are the result of teratogens (alcohol, prescribed and recreational drugs, maternal infections and illnesses, exposure to environmental toxins

and radiation) or abnormalities of the fetal environment that deform or disrupt the developing fetus (e.g. constraint and amniotic band disorder). Teratogens – fetal environmental factors that cause CDs – may be chemical substances, physical agents or infections, and are more common in MLICs where the potential for exposure is higher and there are fewer preventative measures in place.[14]

The global lack of consensus on terminology related to CDs has plagued the medical genetics sector and resulted in lower priority being given to this healthcare issue. In 2006, after decades of uncertainty, agreement was reached by international experts on the use of basic terminology at a joint World Health Organization (WHO) and March of Dimes meeting.[15] Participants recommended that the terms 'CDs' and 'birth defects'[a] be used synonymously. Use of the term 'congenital anomaly' was not advised, since it excludes around 40% of functional CDs including non-syndromic congenital disabilities, common single gene disorders and inborn errors of metabolism.[b,12,15]

The limited uptake of this agreed terminology and the copious use of non-equivalent terms has led to confusion, fragmentation of effort and an inability to compare data sets.[b] This has diluted the visibility of the significant contribution of CDs to neonatal, infant and child mortality, and prevented CD data from being evaluated comprehensively. CDs are often undiagnosed or misdiagnosed and the cause of death is wrongly attributed, contributing to under-reporting.[16] The lack of accurate data on CDs has led to an underestimation of the true contribution of CDs to the disease burden.[14,16,17]

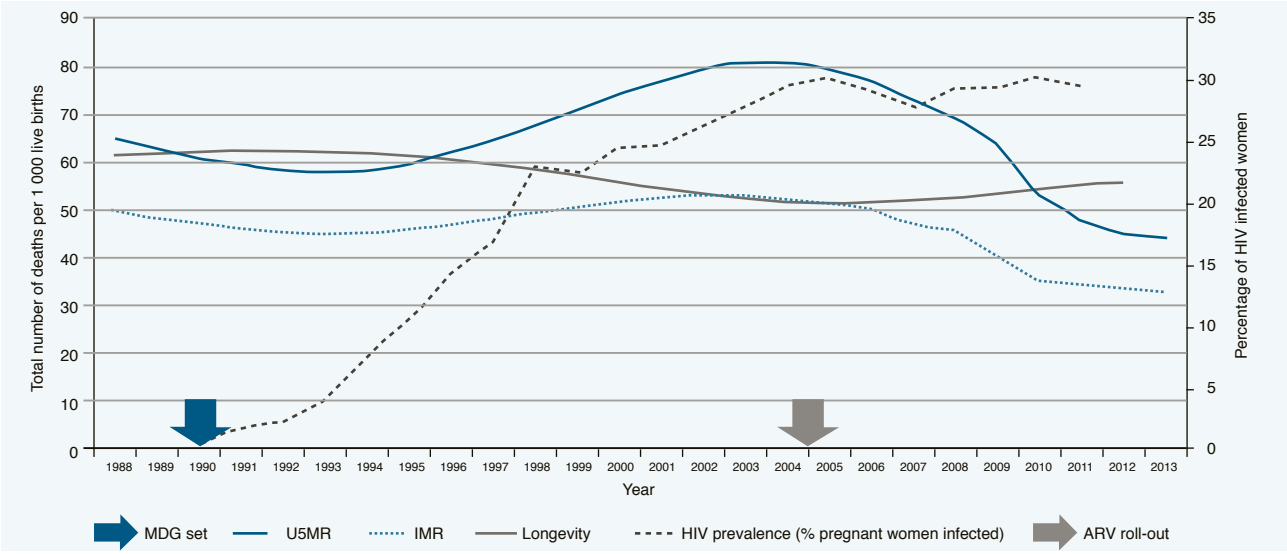
Epidemiological transition

Epidemiological transition occurs when there is a change in population health statistics and pattern of disease in a region or country, resulting from changes in socio-economic, educational, infrastructural and healthcare development.[14] The epidemiological transition of countries has been described extensively using Omran's model,[18] which defines three stages of disease. As mortality rates decrease and longevity increases, countries move from Stage 1 'the age of pestilence and famine' to Stage 2, 'the age of receding pandemics' and into the third stage, 'the age of degenerative and man-made diseases' characterised by low mortality rates and high life expectancy at birth (over 50 years). It is in this third stage that communicable diseases are well controlled or eradicated, and NCDs and degenerative diseases emerge.[18]

Like many MLICs, South Africa is not following Omran's classic model[18] of epidemiological transition that was completed by industrialised, high-income nations decades ago.[19] From 1960 to the early 1990s, infant and child mortality in South Africa declined steadily and longevity increased.[5] Figure 1 plots the U5MR,[20] infant mortality rate (IMR)[20] and life expectancy at birth (longevity) data,[21] and the HIV epidemic (indicated by the percentage of HIV-positive pregnant women)[22] for South Africa for the last 25 years. Life expectancy at birth peaked at 62.33 years in 1992, and in 1993 both the U5MR and the IMR were at an all-time low of 58.2 per 1 000 live births and 45.1 per 1 000 live births respectively.[20,21] All indications were that South Africa was approaching the early phases of transition from Stage 2 (the 'age of receding pandemics') to Stage 3, the 'age of degenerative and man-made diseases' and was set to follow the classical model of epidemiological transition.[5,18]

However, in the mid-1990s, epidemiological transition was interrupted and reversed by the HIV and AIDS and concomitant TB epidemics (Figure 1). As a result of these epidemics, South Africa has seen a counter-transition.[7] HIV prevalence rates, indicated by the infection rate in pregnant women, climbed over the following decade from 7.6% in 1994 to 30.2% in 2005.[22] The U5MR rose dramatically in response, peaking at 80.8 per 1 000 live births in 2003 and the IMR at 53.2 per 1 000 live births in 2002.[20] In 2005, longevity dropped to its lowest level since the 1960s at

Figure 1: Epidemiological transition in South Africa over the past 25 years, as demonstrated by data for childhood mortality,[20] longevity,[21] and the HIV epidemic[22]



Source: Malherbe, 2015.[5]

a Birth defects are defined as abnormalities of structure or function, including disorders of the metabolism, which are present from birth.[15]

b Personal communication: B. Modell, 19 January 2016.

51.56 years.[21] The combination of a newly emerged communicable disease (HIV and AIDS) and the re-emergence of an old infection (TB) with an increasing burden of NCDs has resulted in an additional stage being added to Omran's original concept, called the 'age of emergent and re-emergent infections'.[19,23,24]

Following the roll-out of comprehensive HIV and AIDS interventions in 2004, the HIV and AIDS prevalence rate plateaued at around 30% in the early part of the current decade (see Figure 1).[22] The rapid reductions achieved in infant and child mortality between 2005 and 2011 have resulted in both the IMR and U5MR being lower today than prior to the HIV and AIDS epidemic, at 28 per1 000 and 39 per1 000 live births respectively.[8] South Africa is now back in positive epidemiological transition. However, both the IMR and U5MR have stagnated since 2011, and the neonatal mortality rate (NMR) has stagnated since 2009 despite the continued implementation of HIV and AIDS interventions.[8]

A significant contributor to ongoing high mortality in children are deaths from unnatural causes, causing just over a third (18.5%) of deaths in children aged 1–4 years in 2014.[25] Natural deaths in the same age-group were attributed to intestinal infectious diseases (17.2%), influenza and pneumonia (9.1%) and malnutrition (8.6%), with TB and HIV ranked fourth and fifth.[25] Some neonatal deaths, which contribute the bulk of under-five deaths, are preventable through addressing modifiable factors that are intertwined with social determinants of health. CoMMiC reports that modifiable factors are 30% home-based, including seeking medical attention earlier, failure to recognise severity of illness, and inadequate nutrition.[26] The majority of health system-modifiable factors (80%) relate to health personnel.[26]

The total contribution of CDs to stillbirths[c] in South Africa is unknown. Data from the Perinatal Problem Identification Programme (PPIP) 2012/13 attributed 2.5% of stillbirths in non-tertiary settings and 7.7% of stillbirths in tertiary settings to CDs.[27,28] These data are likely to be an underestimate, especially in primary health care settings due to restricted diagnostics and unavailability of screening. The Lancet Ending Preventable Stillbirths Series Study Group estimates a global median of 7.4% stillbirths attributed to CDs based on reliable data from 18 countries.[28]

However, the role and contribution of CDs to the ongoing high level of mortality is not visible in the available data.

Congenital disorders and epidemiological transition

During the process of epidemiological transition, CD deaths remained invisible, essentially 'buried' among deaths due to communicable diseases, and only emerging as these diseases were adequately controlled.[16] As industrialised countries moved through the second stage of epidemiological transition, there was a slight decrease in CD birth prevalence and deaths due to fetal environmental factors, essentially teratogens.[14] This was because of improved care and prevention strategies for these disorders. However, since 85–90% of CDs have a genetic or partially genetic aetiology, their birth prevalence and resulting mortality remained high.[14] Deaths from these CDs became proportionately greater in overall neonatal, infant and child mortality as deaths from communicable diseases reduced. As industrialised countries completed the second stage of epidemiological transition, CDs emerged and have remained a leading cause of child death in these nations today.[29,30]

CDs attained public health significance in these industrialised nations in the early 1960s when they moved into the third stage of epidemiological transition.[14,18] This was demonstrated in a comparative study undertaken by McKeown[30] of death rates in England and Wales for 1901 and 1971, shown in Table 1. An overall reduction of 68% was seen in the death rate for all diseases over the 70-year study, including a 90% reduction in infectious diseases. Death rates for NCDs decreased by 45% overall, but the number of CD deaths remained the same.[30] This was due to the mainly genetic cause of CDs, which cannot be changed, resulting in CDs contributing a greater proportion of deaths as overall mortality decreased.

Table 1: Standardised death rates (per million of population) for England and Wales in 1901 and 1971

	1901	1971	% Reduction
Infectious Diseases			
Airborne Diseases			
Respiratory infection	2 747	603	78
Pulmonary TB	1 268	13	99
Whooping cough	312	1	100
Measles	278	0	100
Scarlet fever and Diphtheria	407	0	100
Smallpox	10	0	100
Upper respiratory tract infections	100	2	98
Sub-total	5 122	619	88
Food and Water-borne Diseases			
Cholera, Diarrhoea and Dysentery	1 232	33	97
Non-respiratory TB	544	2	100
Typhus, Typhoid	155	0	100
Sub-total	1 931	35	98
Other Infections			
Sub-total	1 415	60	96
90% Overall Reduction for Infectious Diseases			
Non-communicable diseases			
Birth defects	126	127	0
Perinatal problems	1 249	192	85
Heart disease	1 186	1 688	- 42
Rheumatic heart disease	487	88	92
Cancer	844	1 169	- 39
Other diseases	4 598	1 406	69
Sub-total	8 490	4 670	45
Overall reduction for non-communicable diseases 45%			
Total	16 958	5 384	68
68% Overall Reduction in Death Rate of All Diseases			

Source: McKeown, 1976.[30]

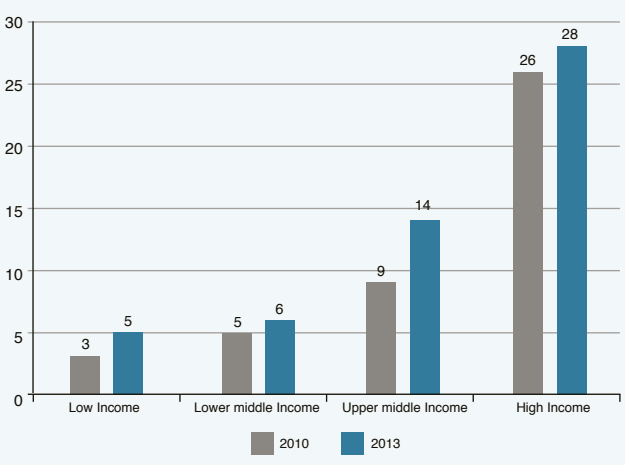
A further example of the increasing proportion of child deaths from CDs is shown in Figure 2, which shows the percentage of deaths due to congenital anomalies using the World Bank Country Classifications[d] according to Gross National Income (GNI) per capita.[4] As GNI increases, the percentage of child deaths from CDs

c In South Africa, a stillbirth is defined as a fetus of at least 26 weeks' gestation and born with no signs of life after complete birth. This definition varies between countries, making data compilation and comparison complex.

d South Africa is classified as an upper middle-income country.

(congenital anomalies only) increases, contributing a greater portion in the higher GNI classification. An increase can be seen in all groups between 2010 and 2013. Today, CDs account for 28% of child deaths in high-income countries and they are the leading cause of death in infants and children younger than five years.

Figure 2: Percentage of under-five deaths resulting from congenital anomalies using World Bank Country Classifications



Source: WHO, 2015.[4]

Figure 3 plots global IMRs for countries against the percentage of infant deaths resulting from CDs, demonstrating that as infant mortality drops, the contribution (proportion) of CDs relative to infant mortality increases. This is particularly noticeable as the IMR drops to between 40 and 50 per 1 000 live births.

It is clear from the literature and mounting evidence that the contribution of CDs to child mortality increases as countries develop, and that MLICs, including South Africa, are following this epidemiological trend.[5,14] The proportion of deaths resulting from CDs in South Africa will rise as overall infant and child mortality decreases.

Congenital disorders in South Africa

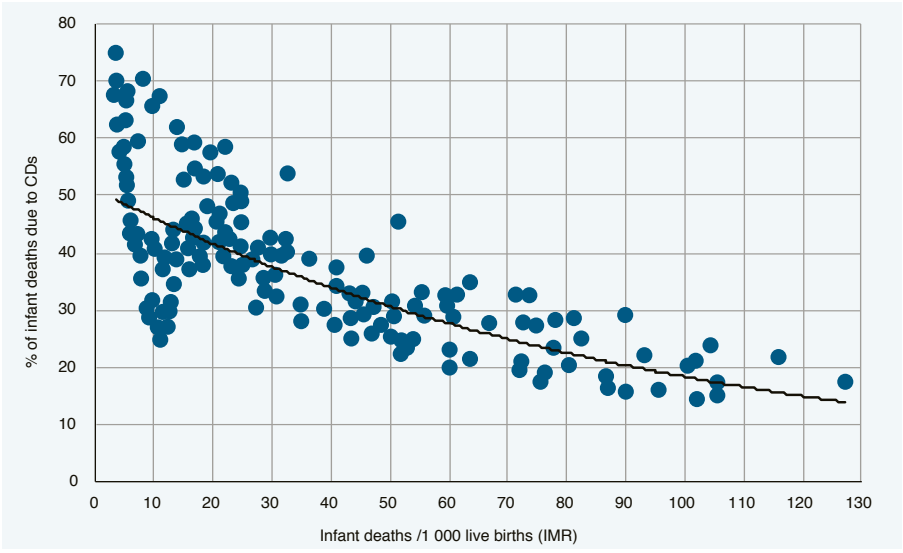
Prior to the HIV and AIDS epidemic in the early 1990s, CDs began to emerge as a healthcare issue in South Africa due to falling child mortality and increasing longevity. A national task force of experts was established in collaboration with the WHO to investigate the need for, and implementation of, services for the care and prevention of CDs. Following wide consultation, the National Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities were published in 2001.[31]

The 2001 National Policy Guidelines[31] outlined goals, objectives, strategies and delivery of clinical and laboratory services appropriate for the care and prevention of CDs in South Africa. Priority disorders were designated, which included Down syndrome, neural tube defects, fetal alcohol syndrome (FAS), albinism, cleft-lip and palate, and club feet. The financial cost to society and to the State resulting from burden of disease was estimated at several billion Rand annually at the time. Personnel requirements to implement these services were specified in the 2001 Guidelines, based on UK criteria, and were later revised using more relevant criteria for South Africa in the Strategic Framework for the Modernisation of Tertiary Hospital Services.[32]

In 2004, the National Guidelines for the Care and Prevention of the Most Common Genetic Disorders, Birth Defects and Disabilities[33] were published, targeting Primary Health Care Providers (PHCPs), and describing common CDs and strategies for their care and prevention.

After this surge of policy generation, the HIV and AIDS and TB epidemics obscured the issue of CDs once more.[5] As a result, the growing commitment and momentum towards CDs as a healthcare issue was redirected to these competing healthcare priorities along with the associated resources.

Figure 3: Relationship between infant mortality and percentage of infants dying from CDs based on global country figures



Source: Modell, 2015.[e]

e Personal communication: B. Modell, 20 August 2015.

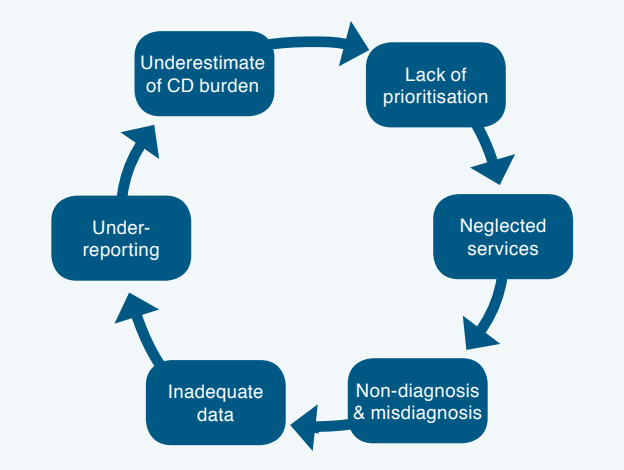
Data modelling of CDs

There is a lack of birth prevalence data for CDs in South Africa, as is the case for many MLICs.[14,16] The overriding factors for this are the limited facilities available and the lack of skilled clinicians to identify and diagnose CDs.[14,16,17] This is exacerbated by the incompleteness of vital registration data and inadequacies of other mortality and morbidity data sources, especially for infants and children.[3,8] To fill this gap, country-specific prevalence estimates are generated using a combination of local data for specific indicators combined with known prevalence rates from more well-resourced countries.[14,16] These modelled data[14] of genetic causes and an estimate of teratogenic causes[f] indicate that a minimum of 6.8% of South African births are affected by CDs.[g] Of these, 80.5% are caused by genetic factors and 19.5% by teratogens. This translates to one in every 15 live births in South Africa being affected by a CD.[5] The proportion of teratogenic CDs is more than the 10–15% expected in MLICs and is one of the highest documented prevalence rates in the world due to the high prevalence of FAS, which is entirely preventable.[14]

Reliable surveillance data provide a vital information tool for policy-makers to plan, implement, monitor and evaluate policy accordingly to prevent adverse health conditions and improve public health. With 6.8% of live births affected by a CD in South Africa, a total of 83 118 live births would have been affected in 2012, based on vital registration data.[34] However, only 2 174 cases were reported via the Birth Defects Collection Tool (BDCT) administered by the Department of Health in 2012.[35] With only 2.6% of the expected CDs being reported, this indicates under-reporting by 97.4% for 2012. When taking into account that only 26% of CDs are diagnosable during the early neonatal period,[36] under-reporting of 90% is still unacceptably high. This is hampering the recognition of CDs as a key contributor to the burden of disease.

The lack of empirical data as evidence for CDs in South Africa prevents policy-makers from accurately assessing the contribution of CDs to the disease burden.[37,38] Figure 4 outlines the cycle caused as a result of this underestimation. Underestimation leads to a lack of prioritisation of CDs, and to CD prevention and care services being neglected. The lack of CD diagnosis due to poor services leads to under-reporting and poor data. Under-reporting contributes to an underestimate of CD deaths and disability. CDs are not considered to be a healthcare priority and the cycle resumes. Modelling is used as a tool to highlight the gap between the expected health need and current services available.

Figure 4: The cycle caused by the underestimation of CDs



Emerging data

Despite the lack of evidence-based data, available mortality data are beginning to reveal the hidden disease burden of CDs. Under-reporting of births and deaths leading to incomplete vital registration data, especially for children, makes it an unsuitable source for monitoring and evaluating child mortality. District Health Information System (DHIS) data, which record deaths in public sector hospitals, also tend to be inadequate, as outlined by McKerrow in 2010.[3] The PPIP is the most detailed source of information on factors contributing to perinatal death and hence child mortality.[3] The 2012/13 PPIP data,[27] representing 75.6% of all DHIS-recorded births in South Africa, indicated that congenital abnormalities[h] have overtaken infection as the third leading cause of death during the first week of life in neonates after deaths from immaturity and hypoxia. Congenital abnormalities accounted for 11.24% and 8.20% of early neonatal deaths in infants weighing >1 000g and >500g compared with 8.84% and 7.44% of deaths respectively from infection.[27] This shift, combined with the stagnation of neonatal mortality since 2009, and of infant and under-five mortality since 2011,[8] speaks to the epidemiological transition in South Africa.

This trend continued in the Western Cape Province (WC) in 2014, with congenital abnormalities ranked as the third cause of early neonatal death in infants weighing >500g and >1 000g.[i] At 10%, deaths in the under-fives from congenital abnormalities in the province are double that recorded in other provinces and nationally.[4,39] The WC neonatal mortality rate is also half the national rate of 11 per1 000 live births,[40] making the province a good example of what will occur in other provinces in the coming decade as healthcare services improve and CDs are revealed.

Following on from the PPIP programme is the Child Healthcare Problem Identification Program (CHILD PIP), which audits child mortality from 28 days to 18 years. In 2005, deaths from congenital abnormalities[j] were mentioned in only 0.3% of cases from the 15 hospitals across six provinces participating in CHILD PIP.[41] CHILD PIP acknowledged this as an underestimate due to the lack of access

f Personal communication: A Christianson, 15 August 2013.

g These modelled estimates are based on national figures published in Appendix B of the 2006 March of Dimes Report.[14] These figures are currently under revision.

h No formal definition is given by the PPIP programme for congenital abnormalities; however, it is understood to refer to obvious structural abnormalities only.

i Personal communication: N. Rhoda, 25 February 2016.

j Although no formal definition of congenital abnormalities is given, the diagnoses made include single gene, chromosomal and multifactorial disorders and post-conception disorders.

to post-mortems and lack of paediatricians to assess (diagnose) the cases.[41] Between 2005 and 2014, mortality data were submitted to CHILD PIP by 198 hospitals across 49 districts. Of the 44 854 deaths recorded,[k] 2.2% cited congenital abnormalities as either the main cause or underlying cause of death. Although higher than the 2005 figure, this too was reported as an underestimate due to the lack of identification of CDs by health workers conducting the audit, and limitations in the cause-of-death categorisation in the current CHILD PIP programme, which is now being rectified by the development of a new data form.[l]

As the U5MR has decreased, the proportion of deaths in the perinatal period has risen.[42] In South Africa, just over 40% of deaths among under-fives occur during the neonatal period.[43] Globally, the contribution of neonatal deaths to under-five mortality is projected to rise from 45% to 52% by 2030.[6] The contribution of CDs to these deaths should be recognised and addressed if child mortality, particularly neonatal mortality, is to be reduced further.

Since available data sets reported only include sub-groups of CDs, the true contribution of CDs to the burden of disease is likely to be higher than estimated.

Congenital disorders and disability

CDs are not merely a cause of child mortality but also of morbidity. For every child who dies as a result of a CD, many survive serious CDs and sustain lifelong mental, physical, auditory or visual disability.[14] The economic cost as a result of this morbidity is considerable. In 2012, 116 000 beneficiaries – caregivers of children older than one year with severe disabilities or disabling chronic illnesses requiring permanent home-based care, including those affected by CDs, acquired conditions and injuries – received means-tested care dependency grants of R1 200 per month.[44] This totals R1.6 billion annually, excluding inflation, adult disability grants and other costs.

In lower-resourced countries, the majority of children born with serious CDs (3.3 million annually) die due to a lack of appropriate care, and a further 3.2 million who survive are disabled for life.[14] Early intervention and relevant care can save the life of the child from a life-threatening serious CD, and cure or ameliorate the degree of long-term disability. Many of these interventions, including one-off surgeries for congenital malformations, are relatively inexpensive compared with the cost of ongoing chronic care for untreated CDs. Many community-based preventative measures are both inexpensive and 'low-tech'.[14] Where appropriate services for the care and prevention of CDs are available, 30% of CD deaths in the first year cannot be prevented. However, 40% of the cases can be cured, mainly by surgery, and 30% survive with disability.[45,46] In South Africa, specialised surgery capacity is limited and unavailable in some provinces, preventing widespread access to such intervention. Strengthening surgical capacity in all areas is required, as both general and specialised surgery could help to alleviate this shortfall.

Interventions must incorporate both prevention and care. As outlined in the 2006 March of Dimes Report,[14] there are three types of prevention: primary prevention, in which CDs are avoided prior to conception through basic reproductive health approaches, including folic acid supplementation; secondary prevention, which aims to reduce the number of babies born with CDs through screening, prenatal diagnosis, avoidance of potentially teratogenic substances during pregnancy and the option of termination of pregnancy; and tertiary prevention, being the early detection, diagnosis, cure and mitigation of CDs after the child is born, including surgical interventions and palliative care. Tertiary prevention is equivalent to care that constitutes diagnosis, treatment, counselling and psychosocial support of those affected by CDs.

In lower-resourced countries, prevention tends to be overemphasised to the detriment of care due to the misplaced myth that care is expensive.[14,16] This may cause those affected by CDs and consequently living with a disability to be marginalised, which undermines their human dignity and human rights. Christianson's mantra, "Care is an absolute. Prevention is the ideal" was coined in 2000.[47] This emphasises both care and prevention (at all levels) as integral components of medical genetic services, and one cannot be neglected at the expense of the other.

In many MLICs, comprehensive services for the care and prevention of CDs are not implemented. In addition to the immense loss of life and suffering of those affected, there is a significant economic cost. Implementation of key interventions can reduce this cost and save lives, as outlined in Table 2. Congenital malformations[m] are the most common type of CD and also the most treatable. Almost half of the congenital malformations such as cleft lip and/or palate and congenital heart defects can be cured through paediatric surgery, but without this intervention, the result is death or permanent disability.

To date, the folate fortification of staple food (maize meal and bread) to reduce neural tube defects (NTDs) – an example of primary prevention – is the only preventative intervention being comprehensively implemented in South Africa. Since fortification began in 2003, a 30.5% reduction in NTDs has been seen.[48] In addition to the obvious reductions in mortality and morbidity, there is also a considerable cost benefit. According to Sayed et al.,[48] with the average estimated cost of treatment being R100 000 per NTD case for the first three years of life, averting 406 cases every year would render a minimum annual saving of R40.6m, offset by the minimal cost of R1.4m per year for the 2% fortification.

If all other interventions were implemented as outlined in Table 2, the burden of genetically determined CDs could be reduced by almost 70% and would generate sizable economic benefits due to the gain of almost three years of healthy life per head of the population.[14,16,46] However, the current static child mortality rates in South Africa are an indication that current interventions being implemented fall far below this level of potential.

k 87.6% of these deaths occurred in children aged five and younger. Personal Communication: M. Patrick, 17 March 2016.

l Personal Communication: M. Patrick, 17 March 2016.

m A malformation due to multifactorial inheritance.

Table 2: Summary of estimated potential effects of interventions for preventing genetically determined CDs

Type of CD	Birth prevalence per 1 000 live births	Intervention	Maximum postnatal lives saved (per 1 000 live births)	Maximum reduction (%)	Estimated average increase in longevity per head of population (years)
Congenital malformations[n]	36.5	Paediatric surgery (Tertiary Prevention/care)	17.70	48.5	1.24
		Folic Acid Supplement (Primary Prevention)	11.50	31.5	0.81
		Prenatal diagnosis (Secondary Prevention)	3.50	9.6	0.25
		Total congenital malformations	32.70	89.6	2.30
Chromosomal disorders[o]	3.8	Family planning (Primary Prevention)	0.75	19.7	0.05
		Prenatal diagnosis (Secondary Prevention)	0.5	13.2	0.04
		Total Chromosomal disorders	1.25	32.9	0.09
Genetic risk factors[p]	2.4	Routine antenatal & neonatal care (Tertiary Prevention/care)	2.40	100	0.17
Inherited disorders (severe, early onset)[q]	11.5	Genetic counselling (Primary Prevention)	1.73	15	0.12
		Neonatal screening (Tertiary Prevention/care)	0.7	6.1	0.05
		Prenatal diagnosis (Secondary Prevention)	1.15	10	0.08
		Total inherited disorders	3.60	31.1	0.25
Total	**54.2**		**39.90**	**73.7**	**2.80**

Source: Christianson and Modell, 2004;[16] Christianson et al., 2006.[14]

Medical genetic services

Interventions to prevent, detect and care for CDs are collectively known as medical genetic services. The aim of genetic services is two-fold: to reduce suffering by offering care to those affected, and to improve health by preventing CDs.[14] These services are key in reducing the contribution of CDs to the burden of disease. By providing the 'best possible patient care' in the prevailing circumstances for those affected by or at risk of CDs, medical genetic services ensure that people with CDs, or those at reproductive risk of having children with CDs, 'can live and reproduce as normally as possible'.[17,49,50]

In many lower-resourced countries, the development of medical genetic services has been driven by epidemiological transition. Governments begin to see CDs as an important public health issue when the IMR falls below 40–50 per 1 000 live births and only limited reductions in child mortality can be achieved by addressing other health issues.[12,16,17,50] With an IMR of 28 per1 000 live births in 2014,[8] South Africa is well past this threshold when medical genetic services should be comprehensively implemented. CDs should be prioritised alongside other NCDs and ongoing interventions against communicable diseases in order to further reduce child mortality and to provide better care for those who are disabled as a result of CDs.[5] When the IMR reaches 20 per 1 000 live births (the MDG 4 target for South Africa), CDs will emerge as a leading cause of death in infants.[12]

Medical genetic services in South Africa

Since the early 1970s, the mainstay of medical genetic services in South Africa has been the work of human genetics departments at major academic centres and medical schools in urban areas, starting in Johannesburg and Cape Town.[51] Access to these services was limited mainly to urban areas, with some outreach into rural areas being conducted by the academic centres.

Services improved following the publication of the Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities in 2001.[31] The number of posts supported by the National Health Laboratory Service increased in response to the policy.[51] However, implementation continued through the established framework of academic centres, rather than through the integration of services into primary health care and the extension of clinical genetic services beyond urban areas, as was recommended in the 2001 Guidelines.

As services for HIV and AIDS developed over the past decade to combat the epidemic, tertiary medical genetic services were neglected.[5] By severely limiting the implementation of the 2001 policy guidelines, the lack of investment in medical genetic services has resulted in insufficient trained personnel, inadequate capacity at all levels, and severely compromised laboratory services.[5,51] In 2013, South Africa was reported as the only country of eight emerging economies evaluated where positive development in improving medical genetic service structures had ceased, and indeed retrogressed.[37]

n Obvious structural abnormalities/malformations due to multifactorial inheritance.

o A structural or numerical abnormality of the chromosomes.

p G6PD deficiency and Rhesus haemolytic disease of the newborn.[14]

q Single gene disorders, including autosomal-dominant, autosomal-recessive, sex-linked inheritance and mitochondrial disorders.

The framework of medical genetic services across the continuum of health care in South Africa is shown in Table 3. This demonstrates how interventions to prevent and care for CDs may be integrated into maternal and child care (e.g. comprehensive antenatal care) and highlights current gaps in implementation.

Table 3: Overview of medical genetic services across health care in South Africa (X=service in place in SA; S= service required in SA)

Type of Prevention/ Care	Intervention	1° Health Care			2° Health Care	3° Health Care	
		Clinic	Community Health Centre	District Hospital	Regional Hospital	Provincial Tertiary Hospital	Academic Hospital
Primary Prevention: Pre-conception care ensuring individuals born free of CDs and not damaged in early embryonic period	**Family planning**	X	X	X	X[r]	X[r]	X[r]
	Optimising women's diet:[s] • Folic acid supplementation (5mg daily)[t] • Iron (200mg daily) • Alcohol/Smoking (education)	X	X	X	X	X	X
	Pre-conception screening	S[u]	S[u]	S[u]	X	X	X
	Maternal infections:[v] Detection and treatment (primarily syphilis)	X	X	X	X	X	X
	Treating health conditions:						
	• Diabetes mellitus		X	X	X	X	X
	• Epilepsy		X	X	X	X	X
	• DVT or cardiac conditions (Wafarin)			X	X	X	X
	Genetic counselling (if required)		S[w]	S[w]	X	X	X
Secondary Prevention: Reducing the number of children born with CDs	**Screening:**						
	Ultrasound		S	S	X	X	X
	Advanced maternal age screening	S	S	S	S	X	X
	Pre-natal diagnosis (amniocentesis, chorionic villus sampling, cordocentesis)				X	X	X
	Genetic counselling and psychosocial support		S[w]	S[w]	S[w]	X	X
	Options: • Therapeutic • Termination of pregnancy		S	X	X	X	X
Tertiary Prevention/Care: Early detection, cure, amelioration and care once a child is born with a CD	**Early diagnosis:**						
	• Examination of every newborn by trained observer (top to toe)		S	S	X	X	X
	• Biochemical screening (Hypothyroidism)		S	S	S	S	S
	Care interventions:						
	• Medical/therapeutic		X	X	X	X	X
	• Surgery			X[x]	X[x]	X[x]	X[x]
	• Habilitation[y]			X	X	X	X
	• Palliative care			X	X	X	X
	• Genetic counselling and psychosocial support		S[w]	S[w]	X[w]	X	X

r Family planning is associated with specialist services in these secondary and tertiary hospitals although it is not listed as an official service.

s Mandatory iodisation of table salt (40–60ppm) was introduced in South Africa in 1995 to prevent iodine-deficiency disorders.

t Mealie meal and wheat flour have been fortified with folic acid in South Africa since 2003.

u Pre-conception screening at the level of community health centres and district hospitals should include screening for advanced maternal age, taking a family history and relevant referral.

v The rubella (German measles) vaccine is available only in the private sector in South Africa.

w Genetic counselling for common disorders such as Down syndrome and spina bifida.

x This may be limited to general surgery in some provinces where specialised surgery (e.g. cardiac, cranofacial, etc.) is currently unavailable. Some CDs may require only general surgery (e.g. Meckel's diverticulum), whilst others require more specialised surgical intervention (e.g. cleft lip and/or palate).

y For example, occupational, speech and physiotherapies.

Table 4: A comparison of medical genetics services capacity in 2001 and 2015

Category	Recommended 2003[32]		2001[31]		2015	
	Number	Ratio (Pop=46 13m)[52]	Number[2]	Ratio (Pop=44 82m)[52]	Number	Ratio (Pop=54 96m)[34]
Medical geneticists	20	1 per 2m	4	1 per 11.2m	12[z]	1 per 4.9m
Genetic counsellors	80	1 per 580 000	<20	1 per 2.2m	8[aa]	1 per 8.4m
Medical scientists/technologists	100	1 per 450 000	50	1 per 900 000	26[ab]	1 per 2.1m

Medical genetic services are now at a lower base than in 2001, as outlined in Table 4. The 2003 recommended human capacity requirements[32] to be trained and in-post by 2010 remain unfulfilled. Today there are 12 medical geneticists, compared with four in 2001 and the 20 recommended by 2010.

Of the 14 genetic counsellors practising today, only eight practise in State services, compared with 20 in 2001 and the 80 recommended. Since existing posts were frozen and no new posts were created to accommodate newly qualifying genetic counsellors, many have been forced to leave the service or the country, or to work in private practice. No provision was made for genetic counsellors in the Occupational Specific Dispensation (OSD), a government initiative aimed at attracting and retaining skilled employees through improved remuneration. Budget cuts have also reduced diagnostic laboratory personnel numbers to unsustainable levels and equipment has not been upgraded or maintained.[5,51] Many practitioners have left, retired or emigrated due to a high service workload, limited opportunity to undertake research, and the inability to perform their tasks satisfactorily due to inadequate medical genetic laboratory services. To reverse this, adequate staffing and modern equipment are required along with the necessary training to ensure the translation of this technology is appropriate to the country's needs and circumstances.

The lack of access to health workers is possibly the greatest constraint across the health system in terms of South Africa achieving health goals,[26] including the MDGs. Rectifying the shortfalls in specialist healthcare professionals in the medical genetic services sector is critical.

The Medical Genetics Education Programme (MGEP) is a distance-education postgraduate training course for nurses and rural medical officers. This equips in-post healthcare professionals with basic knowledge and skills to identify and diagnose common disorders, counsel patients and to refer those affected by CDs appropriately, providing an additional supporting capacity for medical geneticists and genetic counsellors. Between 2004 and 2013, over 1 000 healthcare providers, mainly labour ward nurses, were trained through the MGEP course held countrywide.[ac] Today, fewer than 100 remain in services for the care and prevention of CDs. The lack of continued government support for this training, including financial, trainee contact and uptake of these skills by facility management, has forced trainees to discontinue their genetic nursing role and move to other fields. This has had a direct negative impact on the national surveillance of CDs via the BDCT, as many MGEP-trained labour ward nurses, together with midwives, obstetricians and paediatricians, are the frontline healthcare professionals encountering CDs in the continuum of care.

Legislative and regulatory framework

The World Health Assembly (WHA) call in 2010[13] to prioritise CDs as a healthcare issue through Resolution 63.17 was fundamental for medical genetic services worldwide. WHA 63.17[13] recognised the importance of CDs as a cause of stillbirths and neonatal deaths, and their contribution to under-five mortality, and it is recognised that for MDG 4 to be achieved, "accelerated progress in reducing neonatal mortality including the prevention and management of birth defects" was required. Although South Africa is yet to respond to WHA63.17,[13] a number of other international treaties and protocols of relevance to CDs have led to the development of equivalent national legislation. Table 5 lists international treaties and conventions that included content of relevance to CDs, many of which are foundational for national legislation.

South Africa is well placed to respond to WHA 63.17[13] since a comprehensive, national legislative framework already exists for the provision of medical genetic services for the care and prevention of CDs. Relevant national legislation is outlined in Table 5. The Constitution of the Republic of South Africa[53] provides for fundamental rights to life, equality, dignity, freedom and security of the person, and education. The socio-economic right for all to access healthcare services, including reproductive health care, is provided subject to the concept of progressive realisation.[ad] Every child – including those with CDs and disabled as a result – has the right to 'basic nutrition, shelter, basic healthcare services and social services' (section 28, 1c), but these rights are not subject to progressive realisation.

The provision of medical genetic services is specified in the National Health Act (NHA) 61 of 2003 through a clear directive in Chapter 3, under "Main functions of the National Department" in section 21 (2) (b) (vii) as follows:

> The Director-General must, in accordance with national health policy, issue and promote adherence to, and norms and standards on health matters including genetic services.[54]

Also of relevance to CDs in the NHA are epidemiological surveillance, management, prevention and control of NCDs, and the health needs of vulnerable groups including children and the disabled.[54] Other key national legislative instruments of relevance to CDs are outlined in Table 6.

z No medical geneticists are employed by the State in Gauteng. Personal communication: A. Krause, 11 February 2016.

aa Of these eight genetic counsellors, three are employed full-time directly by the State, three full-time by tertiary institutions, and four are employed part-time, plus six in private practice. Personal communication: T. Wessels, 25 February 2016.

ab NHLS academic medical scientists only. Personal communication: H. Soodyall, 27 July 2015.

ac Personal communication: D. Tshikedi, 2 October 2013.

ad Defined as recognising that economic and social rights can only be achieved over time, subject to the availability of resources.

Table 5: International treaties, conventions, declarations and protocols of relevance to medical genetic services

Document	Article/ Rule/Overview
World Programme of Action Concerning the Disabled (1982)	Prevention, rehabilitation and equalisation of opportunities
Standard Rules on the Equalization of Opportunities for Persons with Disabilities (1993)	1 Awareness-raising 2 Medical care 3 Rehabilitation 4 Support service 5 Accessibility
United Nations Convention on the Rights of the Child (signed 1993 and ratified 1995)	2 No discrimination 6 Right to life 23 Disabled child 24 Healthcare 26 Social Security
International Covenant on Economic, Social and Cultural Rights (1966) (signed 1994 and ratified 2015)	12 Physical and Mental Health
United Nations Millennium Declaration (signed 2000)[1]	Goal 4: Reducing under-five mortality by two-thirds by 2015
United Nations Convention on the Rights of Persons with Disabilities (signed and ratified 2007)	5 Equality/non-discrimination 6 Women with disabilities 7 Children with disabilities 8 Awareness-raising 9 Accessibility 10 Right to life 19 Living independently 20 Personal mobility 23 Respect for home and family 25 Health 26 Habilitation and Rehabilitation
African Charter on the Rights and Welfare of the Child ('Children's Charter') (signed 1997 and ratified 2000)	5 Right to life 13 Protection of physically/mentally disabled to ensure dignity 14 Physical/ mental health and healthcare
The New Partnership for Africa's Development (2001)	Healthcare provision and delivery
African Youth Charter (signed and ratified 2009)	16 Health 23 Girls and young women 24 Mentally/physically challenged youth
World Health Assembly Resolution 63.17 (signed and ratified 2010)[11]	Urges member states to address CDs as a healthcare issue through specific actions

Table 6: Key national legislation of relevance to medical genetic services

Title	Overview	Sections relevant to CD
Constitution of the Republic of South Africa (108 of 1996)[53]	Chapter 2 – Bill of Rights	• 9 Equality • 10 Human dignity • 11 Life • 27(1)(a) Access to healthcare services, including reproductive healthcare • 28 (1)(c) Every child has the right to basic healthcare services
Health Professions Act (56 of 1974)	Regulates the health professions through the Health Professions Council of South Africa	
National Health Act (61 of 2003)[54]	Framework for a structured and quality uniform health system	• 4(3)(a) Free healthcare to pregnant/breastfeeding women, children under six not members/beneficiaries of medical aid schemes (c) free termination of pregnancy • 21(2)(b)(vii) Genetic services • 21(2)(k) and 25(2)(w) Management, prevention and control of communicable and non-communicable diseases • 23(1)(a)(ix) and 27(1)(a)(ix) Epidemiological surveillance and monitoring of national and provincial trends • 21, 23, 25, 27 Implementation of national/provincial policy and compliance • 39(2)(a)&(d), 70(2)(d) Health needs of vulnerable groups including children and people with disabilities • 48 Development and provision of human resources in national health system • 52 Regulations relating to human resources • 70 Identification of health research priorities
Choice on Termination of Pregnancy Act (92 of 1996)	Law related to abortion	• 2(b)(ii) and minors 5(5)(a)(ii) Termination of pregnancy (ToP) between 13–20 weeks inclusive if substantial risk that the fetus would suffer from a severe physical or mental abnormality • 2(c)(ii) and minors 5(5)(b)(ii)ToP after the 20th week if the continued pregnancy would result in a severe malformation of the fetus
The National Health Laboratories Service Act (37 of 2000)	Laboratory services for the public health sector	• 4 and 5(1) Cost-effective and efficient health laboratory services including training
Mental Health Care Act (17 of 2002)	A legal framework for mental health in South Africa with an emphasis on human rights	
The Nursing Act (33 of 2005)	Regulates the nursing profession through the South African Nursing Council	
Children's Act (38 of 2005)	Protection of children and their rights	• 11 Children with disability or chronic illness • 156 (1)(G) Care and protection
Social Assistance Act (13 of 2004)	Rendering of social assistance	• 7 Care dependency grants • 9 Disability grants

National policy

The National Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities[31] and the National Guidelines for the Care and Prevention of the Most Common Genetic Disorders, Birth Defects and Disabilities[33] are the only two policy documents that focus solely on CDs. In 2014, a process of revision of the 2001 Policy Guidelines was initiated and is due for completion in 2016.

A new edition of the Guidelines for Maternity Care in South Africa was published in 2015,[55] replacing the 2007 edition. This contains relevant content on the identification of mothers at high risk of having babies with a CD, as well as essential information for primary prevention of CDs and referral to genetic services.

Implementation of the 2001 Policy Guidelines,[31] and therefore of the underpinning legislation, has been fragmented, especially in the past decade. The lack of recognition for the contribution of CDs to the disease burden has resulted in the exclusion of comprehensive interventions from national strategies. The lack of integration of key interventions is noticeable in the National Department of Health's Strategic Plan for Maternal, Newborn, Child and Women's Health and Nutrition in South Africa 2012–2016.[56] While CDs are mentioned as a cause of neonatal death and as contributing to 15–20% of children affected by long-term/chronic health conditions "not receiving the care they require", no responding interventions are outlined.[56] In other documents, individual CDs or categories such as mental health disorders are recognised in the National Department of Health's Strategic Plan 2014/15–2018/19,[57] but with no acknowledgement of the genetic predisposition of such conditions.

CDs are the first NCDs experienced by people – infants and children.[12] However, they are not contextualised as such in national strategies and interventions to address the growing NCD disease burden. In the 2nd Triennial Report of the Committee on Mortality and Morbidity in Children (CoMMiC),[26] CDs are included under long-term health conditions in children together with acquired childhood conditions resulting from infections. This precludes the use of the term 'NCD', effectively burying CDs beneath communicable disease once again.

Conclusions and recommendations

CDs are currently not recognised as a healthcare issue in South Africa. Thus, their contribution to the disease burden is currently underestimated, and the impact of interventions for their prevention and care is not considered. Instead, those born with and dying from CDs are largely overlooked and those surviving with disability are largely ignored, as care is not being provided to this most vulnerable group. Despite the lack of data due to poor national surveillance, CDs are beginning to emerge as a significant cause of mortality in children. Data from child mortality audit programmes indicate the growing contribution of CDs to neonatal death and to deaths in children under five years of age. Following the epidemiological trend of industrialised countries, the contribution of CDs to the disease burden will continue to increase in South Africa as the country develops, until they eventually constitute the leading cause of child death and disability. By not addressing this issue comprehensively now, many lives will be lost unnecessarily and others will survive with lifelong disability as the result of serious CDs. There is also a significant economic cost associated with CDs. Up to 70% of the deaths and the disability caused by CDs can be prevented or mitigated through relevant interventions.[45,46]

South Africa has already passed the point at which other nations have identified the need to develop comprehensive medical genetic services in order to reduce child mortality further. This is largely a consequence of the abating HIV and AIDS and TB epidemics which have buried CDs as a health issue. While the control of these epidemics must continue, it cannot be at the expense of other child healthcare needs if child mortality, including neonatal deaths, is to be further reduced.[5,7]

While a good legislative framework provides for genetic services in South Africa, the significant shortfall in implementation indicates that this intention has been lost in translation. Medical genetic services currently available are inadequate in terms of capacity and infrastructure at all levels and far from the seamless continuum of care required. While the implementation of accessible and relevant medical genetic services for the care and prevention of CDs is essential to contribute to reducing static mortality rates further in South Africa, such interventions must also plan for morbidity and ongoing treatment of those affected. Such interventions have major economic implications for South Africa, and the CD contribution to the burden of disease should be addressed holistically.

If South Africa is to meet the Sustainable Development Goal (SDG) 3[58] target to end preventable deaths in newborns and children, and to reduce the U5MR to at least 25 per 1 000 by 2030, CDs must be comprehensively addressed. Reducing premature mortality from NCDs by 2030 will require CDs to be contextualised as a NCD in South Africa, in alignment with the international definition of NCDs. The SDG goal for universal health coverage and access to quality essential healthcare services can only be achieved if relevant medical genetic services for the care and prevention of CDs are made available for all South Africans.[58]

The re-engineering of the healthcare service and the NHI initiative[59] provide opportunities for the rebirth of medical genetic services, and for rectification of their currently compromised state. Their integration as part of services for women's, maternal and child health would allow medical genetic services to develop throughout the continuum of care in all appropriate stages of life. Such services are vital to uphold the dignity and constitutionally and legally enshrined rights of those affected by CDs.[5,60]

Priority actions include:

- Increased political will and financial commitment – This should be accompanied by appropriate CD-related expertise on ministerial and government committees dealing with the neonatal/infant/child mortality and the development of women, maternal and child health services.
- Improvement of national surveillance, patient registries and monitoring of CDs – Linked to existing systems for sustainability, these should be accompanied by ongoing training to increase coverage and accuracy of CD data identification and documentation.
- Capacity-building – The education and training of healthcare professionals and the creation of related posts is required at all levels, especially for staff in primary health care facilities.
- Increased community education and awareness – Such programmes are required to ensure awareness, understanding and knowledge of available services and how to use them.
- Role of lay advocacy/patient support groups – These need to be recognised, supported and strengthened to partner with government and the medical genetics community.

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Post-Script to Chapter 6

Following publication of this paper the PhD examiners identified specific edits that would further improve the quality of the paper. While we acknowledge that the version of the paper published by the journal will remain unchanged we would like to specify the following amendments:

- Page 57, Figure 1, Source, amendment: Malherbe *et al*, 2015 instead of Malherbe, 2015.
- Page 58, **column 1, paragraph 3, line 1-2, amendment: '**A significant contributor to ongoing high mortality in children are deaths from unnatural causes, causing just over a third (**34.3%)** of deaths in children aged 1-4 years in 2014.' The published percentage of **18.5%** referred to children aged 5-9 years.

Chapter 7: Contribution of congenital disorders to under-5 mortality

This article has been published in the South African Medical Journal.

Malherbe HL, Aldous C, Christianson AL, Woods D.S. Contribution of congenital disorders to under-5 mortality. Afr Med J. 2016 Aug;106(8):745. doi:10.7196/SAMJ.2016.v106i8.11129.

Chapter 7 continues the theme of CDs and child mortality with this letter to the editor responding to an article publishing child mortality data for a specific region of the Western Cape (1). The issue that is tackled in this article is terminology related to CDs and the use of non-equivalent terms used interchangeably. This results in sub-sets of CDs being reported as the totality of CDs, which further contributes to the underreporting of CDs and an underestimate of the true contribution of CDs to the burden of disease. In this specific case, the term congenital abnormalities is used, which relate to chapter XVII of the International Classification of Diseases (ICD-10) (2). This includes development structural abnormalities only and excludes a large portion of CDs (particularly single gene disorders and environmentally caused CDs) found elsewhere in the ICD-10 system (3). It is important that this incomplete reporting of CDs is acknowledged and uniform terminology is consistently used for reporting purposes.

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Contribution of congenital disorders to under-5 mortality

To the Editor: The article 'Where do children die and what are the causes?', which appeared in the April 2016 issue of the *SAMJ*,[1] provides an overview of the causes of death in under-5 children in the Metro West geographical service area of the Western Cape for 2011. It highlights the proportion of under-5 deaths from congenital abnormalities (obvious structural abnormalities), which are particularly prevalent in early neonatal mortality – a close third (9.6%) of in-hospital deaths after hypoxia (10.0%) and immaturity (40.6%) according to the Perinatal Problem Identification Programme (PPIP) data.[1] In the Local Mortality Surveillance System in-hospital data, congenital abnormalities are ranked as the second (13.5%) cause of early neonatal death after prematurity (35.8%).[1]

Although already prominent as a cause of death, congenital disorders (CDs) may collectively contribute to a greater proportion of child deaths than reported. In the study, congenital abnormalities relate to chapter XVII: Congenital malformations, deformities and chromosomal abnormalities in the *International Classification of Diseases* (ICD-10) and are aggregated to the Burden of Disease list of causes.[1-3] Limited to developmental structural abnormalities only, this excludes a significant portion of CDs found elsewhere in the ICD-10 system (e.g. congenital syphilis A50; haemophilia D66 - 68; oculocutaneous albinism E70.310).[3] This ICD-10 coding fragmentation has exacerbated global confusion around terminology related to CDs.[4] In 2006, international agreement was reached on the synonymous use of the terms CDs and birth defects, defined as abnormalities of structure or function, including metabolism, present from birth and manifesting at birth or later in life.[5] However, use of inequivalent terms, such as congenital abnormality, continues. Consequently, data for subsets of CDs are often interpreted as the totality of CDs when it is not the case. If single-gene disorders, accounting for 30.0% of CDs (B Modell – personal communication, 2016), were pooled with congenital abnormalities in the study by Reid *et al.*,[1] a greater proportion of under-5 deaths may be attributed to CDs.

CDs are also significantly underestimated, as many remain undiagnosed or are misdiagnosed, with the incorrect cause of death due to the lack of trained clinicians,[6-8] as acknowledged by the Child Healthcare Problem Identification Programme.[4,9] Undiagnosed CDs may be the underlying cause of death in a number of cases assigned to other causes (including 'ill-defined') or comorbidity in the study, as infants born with CDs, such as congenital heart defects, may be more susceptible to infection.

Honein *et al.*[10] reported that CDs are more than five times as likely to occur among very preterm infants (24 - 31 weeks) compared with term infants (37 - 41 weeks), resulting in 16.0% of preterm infants having a CD. A significant portion of deaths assigned to 'prematurity' in early neonatal deaths in the study may therefore be undiagnosed CDs, which are predisposed to preterm birth.

The relative frequency of CDs should be noted and investigated in light of the abovementioned factors contributing to their under-reporting, particularly as the majority of CD-related deaths occur during the first 5 years of life. As the proportion of deaths from CDs increases along with epidemiological transition – seen in the dramatic decrease in HIV-related deaths – the challenge of CDs will continue.[11] Possible areas for further study include comparison with other provincial populations, analyses of preventable CDs (e.g. fetal alcohol spectrum disorder) and prenatal diagnosis of serious CDs.

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Part Three: Modelling data for South Africa

In Part Three the focuses shifts to generating modelled data for SA. A finding in all previous parts of the study is the lack of empiric data for CDs in SA. Without these data there is no evidence to demonstrate the disease burden represented by CDs. In the interim before improved surveillance systems are available in SA, we have to consider modelling estimates of the expected numbers of CDs – that we should be seeing in SA. Modelled estimates provide a tool for measuring services until such a time when they are no longer necessary – when surveillance systems are collecting complete data.

Modelled estimates for CDs have been published before as part of the March of Dimes Global Report on Birth Defects in 2006 (1). These national figures were based on demographic estimates sourced mainly from World Population Prospects. The approach taken in this study collates and uses local demographic data at the provincial level, using the revised Modell Global Database (MGDb) and its inherent improved modelling techniques. While these results cannot be compared with the 2006 estimates, they are considered more accurate and realistic. Estimates were developed for four specific groups of CDs with endogenous causes (single gene disorders, chromosomal disorders, malformations and additional conditions) and results provided at a national level. This chapter sets the stage for future in-depth articles for specific disorders and provincial variations.

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Chapter 8: Epidemiological data for congenital disorders in South Africa

This article is submission ready for the Journal of Health Policy and Planning.

Malherbe H, Aldous C, Christianson A, Darlison M, Modell, B. Epidemiological data for congenital disorders in South Africa.

Modelled epidemiological data for congenital disorders in South Africa

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Keywords: Congenital disorders, birth defects, medical genetic services, surveillance systems, infant mortality rate, modelling, South Africa.

Key Messages:

- There is a lack of empiric data for congenital disorders (CDs) in South Africa, leading to underreporting and an underestimation of the CD disease burden, preventing the prioritisation of relevant medical genetic services.
- Modelled data plays an important interim role in highlighting the CD burden of disease until surveillance systems are improved.
- Methods from the Modell Global Database of Congenital Disorders (MGDb) were applied in South Africa to model baseline estimate for endogenous CDs for 2012 in the absence of care. The 2012 actual birth prevalence was estimated to evaluate the effect of present interventions compared with baseline estimates.

- Access to relevant interventions (estimated at 30%) reduced the number of births affected by CDs and the number under-5 deaths, and increased the number of affected infants surviving to age 5.

Acknowledgments: Thank you to: Professor Rob Dorrington, Centre for Actuarial Research (CARe), University of Cape Town for providing demographic data for use in this study; Professor Debbie Bradshaw, Burden of Disease Unit, South African Medical Research Council for conceptual and expert advice; and Statistics South Africa (StatsSA) for providing the 2013 data sets -although these StatsSA data were not used in the final modelling process they were a key component in the decision making process at the data gathering stage of this study.

Abstract

Monitoring and surveillance data for congenital disorders (CDs) is necessary for the development of targeted medical genetic services at a local, regional and national level. Empiric data is lacking for South Africa, with CDs underreported by over 98%. This is contributing to (a) underestimation of the disease burden of CDs, and (b) failure to prioritise services appropriately. Modelling offers a viable option to provide estimated figures, until improved surveillance systems can make good this shortfall.

In this study, methods from the Modell Global Database of Congenital Disorders (MGDb), including birth prevalence data from well-established surveillance systems, were used with local demographic data to generate 2012 baseline country estimates for endogenous CDs in the absence of care. The 2012 actual birth prevalence was then estimated using the MGDb approach to evaluate the effect of present interventions compared with baseline estimates. Access to relevant health services, and so the impact of interventions, was quantified using the infant mortality rate (IMR) as a proxy.

Baseline estimates indicated a birth prevalence of 30.5 affected births per 1 000 live births. Half of the 35 675 died under-5 years, with 25% (n=9 535) dying in the first month of life. With access to care estimated at 30%, 1 860 affected births were avoided as a result of pre-conception and pre-natal interventions. Birth prevalence was reduced by 1.1 per 1 000 live births. Overall survival increased by 12% (n=3235), and 5 010 under-5 deaths were prevented.

This study highlighted the utility of modelled data in profiling the disease burden of CDs in South Africa, and the impact of medical genetic services in reducing mortality and improving the quality of life of those affected. Further study includes analyses of modelled estimates (a) for specific CDs, (b) in specific provinces of SA, and (c) costing of specific interventions.

Introduction

Health data monitoring and surveillance is crucial to enable timely and appropriate public health responses to reduce disease burden (1). These observed data provide a factual basis for rational decision making by policy makers, directing research and policy to address present and future needs, prioritising health issues and allocating resources (2). The Centers for Disease Control (CDC) defined epidemiologic surveillance in 1986 as "*the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice*" (3-5). This has evolved into public health surveillance, which provides an evidence-based approach to defining health needs, and implementing focused programmes in response. It is an integral part of health needs assessment (HNA) – a rational, epidemiology-assisted approach providing information for the planning, introduction and modification of health care services to benefit the health of populations (6). Public health surveillance includes the monitoring of communicable and non-communicable diseases (NCDs), health interventions, injuries, child growth and nutrition, and occupational health (2, 7). It is also undertaken for congenital disorders (CDs), the first NCD experienced by people (8).

CDs, defined as abnormalities in structure or function, including metabolism, present from birth (9), include chromosomal disorders, congenital malformations, single gene disorders and disorders with multifactorial causes. Surveillance is required to target medical genetic services for care and prevention at a local, regional and national level (9, 10). Established surveillance systems monitor trends and evaluate ongoing programmes, with the difference between birth and population prevalence used as an indicator of effectiveness of care, and the number of affected births as an indicator of effective prevention (6). In Iran, surveillance showed a 20% reduction in births affected by thalassemia in 2005 compared to expected (modelled) births following implementation of a prevention programme (11). Expected birth prevalence rates were based on modelled figures, due to a lack of empiric data (6, 10). Where no interventions are currently available, surveillance helps prioritise and guide research (12). Clusters of CDs may also be identified, such as those caused by specific teratogens, to prevent a repeat of the thalidomide tragedy of the late 1960s, although this has become a secondary aim of surveillance (13).

In high income countries where CDs are a leading cause of death in childhood (14), robust monitoring and surveillance systems have developed over the past 40 years, although obtaining comprehensive, standardised data remains a challenge (13). In middle and low income countries (MLICs), reliable epidemiological data on CDs is scarce due to inadequate or absent surveillance systems (10, 15, 16). This paucity of

information skews national and global estimates of CDs, resulting in underestimation of their significance as a health care issue (16, 17). This impedes policy development and implementation in MLICs, preventing those affected from receiving the care they require. Challenges faced by MLICs often include a persisting communicable disease burden coupled with emerging NCDs (18). This protracted epidemiological transition continues to mask the burden of CDs, which remain undiagnosed or misdiagnosed and are thus omitted as causes of deaths (15, 18). This is exacerbated by the lack of skilled professionals and by inadequate infrastructure (10, 15-17). Underreporting of CDs prevents an accurate assessment of their burden, resulting in lower funds allocated for surveillance, training of health care professionals and other essential medical genetic services (8).

Lack of empiric data in South Africa

In South Africa (SA) current modelled estimates indicate that one in every 15 births or a minimum of 6.8% of births, is affected by a CD[1](19). Of these, 80.5% have endogenous (i.e. genetic or partially genetic) causes, while 19.5% are caused by teratogens[2]. This indicates that more than 70 000 live births a year are affected by a serious CD[3] (20). However, Lebese *et al* (21) reported only 13 252 CD cases via national surveillance between 2006-2014. This is less than 20% of annual expected CDs reported over a six-year period, and indicates underreporting of 98% compared to expected numbers (19, 21). Datasets known not to be integrated into the national surveillance database administered by the National Department of Health (NDOH) include registries managed by patient support groups and data compiled at health facilities. Death audit programmes, such as the Perinatal Problem Identification Programme (PPIP) and the Child Problem Identification Programme (Child PIP) collate mortality data only. However, many of these programmes report on *congenital anomalies*, based on Chapter XVII of the International Classification of Diseases (ICD-10) system, which includes only chromosomal disorders and congenital malformations (22-24). Often interpreted as the totality of CDs, congenital anomalies are a sub-set, and exclude most single gene disorders and environmentally caused CDs (25, 26). This contributes further to underreporting of CDs.

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[1] Based on the modelled figure of 53.4 per 1 000 live births born annually with a serious genetic CD and estimated figures for teratogens, particularly fetal alcohol syndrome (10) (Professor Arnold Christianson, personal communication).

[2] Teratogens include altered maternal metabolic states (diabetes mellitus, hypothyroidism, iodine deficiency), infectious agents, ingested substances (alcohol, illicit drugs and medications), hyperthermia, environmental pollutants and massive radiation exposure (29).

[3] Serious birth defects are life threatening or have the potential to result in disability (10).

The role of modelled epidemiologic data

Modelled data enables informed policy making and HNA to proceed so that relevant services can be developed where observed surveillance is lacking (6). These modelled data provide the expected numbers of CDs; as empiric data emerges, the need for modelling falls away (6).

In 2006 baseline birth prevalence data were published in the March of Dimes Global Report on Birth Defects (10), to attempt to fill the gap due to inadequate birth prevalence data for CDs at a national and global level. A database (now known as the Modell Global Database of Congenital Disorders – MGDb) was used to generate baseline country estimates in the absence of care, for CDs with endogenous causes using birth prevalence data from well-established CD surveillance systems. A long-term intention has been to expand this method to develop sub-national estimates generated by individual countries using locally sourced demographic data. This study explores the application of MGDb methods at the national level in SA, in order to model baseline estimates for the birth prevalence of endogenous CDs for 2012. The actual birth prevalence was estimated using the MGDb approach to evaluate the effect of present interventions compared with baseline estimates for 2012.

Method

Setting

This desktop, data analysis study was initiated in October 2014 with a consultative meeting at the Centre for Health Informatics and Multiprofessional Education (CHIME), University College London (UCL) with Professor Bernadette Modell and Dr Matthew Darlison of the World Health Organization (WHO) Collaborating Centre for Community Genetics, and Professor Arnold Christianson and Helen Malherbe from SA. Other than a follow-up meeting at CHIME, UCL in November 2015 the study was undertaken in Johannesburg, South Africa.

Premise of the study

The MGDb links reliable birth prevalence data for groups of CDs to population specific demographic data to generate modelled estimates of actual affected births and other relevant outputs. The impact of interventions through access to relevant health services for affected individuals is quantified using the infant mortality rate (IMR) as a proxy for access (26).

Scope of Study

Period of study

Births and deaths occurring in all nine South African provinces were included for the 2012 vital registration year. The year 2012 was the most recent for which data were

available with the greatest degree of certainty. It is also the year subsequent to the observed stagnation of child mortality rates, when no further significant reductions had been observed after a period of rapid reduction (27). The use of annual data for the South African MGDb (MGDb-ZA) is in contrast with the MGDb, which uses demographic data sourced from the World Population Prospects (WPP), which is given mainly in five-year intervals.

Conditions included

Four groups of early onset CDs (presenting before the age of 20) with mainly endogenous causes were included in the MGDb-ZA. Several placeholder conditions are also priority CDs in SA (28). Specific CD groups included:

- **Single Gene Disorders:**
    - Early onset autosomal dominant,
    - autosomal recessive (placeholder condition - oculocutaneous albinism),
    - sex-linked single gene disorders,
    - consanguinity associated disorders.
- **Chromosomal Disorders:**
    - Down syndrome,
    - other trisomies (Trisomy 18 and Trisomy 13),
    - rare autosomal chromosomal disorders,
    - sex chromosomal disorders (Turner and Klinefelter syndromes).
- **Congenital Malformations:** Non-syndromic isolated congenital malformations are divided into five sub-categories:
    - Neural tube defects (NTD)
    - Congenital heart disease (CHD)[4]
    - Oral facial clefts (OFC)
    - Potentially fatal (majority very severe in the absence of care) other malformations: Central nervous system (CNS) not NTD; eye; ear, face and neck; respiratory system; digestive system, abdominal wall defects; urinary system; other malformations; and multiple malformations.
    - Non-fatal (majority less severe in the absence of care) other malformations: genital and limb.
- **Additional Conditions:**
    - Non-genetic CDs excluded from registries and classed elsewhere in ICD-10 system e.g. congenital hypothyroidism due to thyroid

[4] The MGDb category congenital heart disease is the sub-set of congenital heart defects which cause disease (death or disability) in the absence of care.

aplasia/dysplasia, or conditions with an uncertain status e.g. pyloric stenosis and prematurity-associated persistent patent ductus arteriosus.

Conditions excluded

The following conditions were excluded:

- CDs caused post-conception due to an abnormal fetal environment, e.g. maternal illness or exposure to teratogens (29), since these cannot be predicted.
- Non-genetic CDs with functional rather than anatomical effects (e.g. the proportion of cerebral palsy of intrauterine origin): these are usually excluded from congenital anomaly registries.[5]
- Later-onset single gene disorders such as family cancer syndromes or genetically-determined neurodegenerative disorders.
- Disorders due to genetic risk factors. MGDb includes two common early-onset examples, rhesus haemolytic disease and neonatal jaundice due to G6PD deficiency.

Data limitations

The modelled estimates generated represent estimates only for a sub-set of the totality of CDs.

Estimates resulting from the MGDb-ZA are not comparable with SA data from the 2006 Modell Birth Defects Database (10) due to (a) changes in modelling methods and (b) different sources of demographic data.

The MGDb-ZA (like MGDb) uses demographic denominators for live births only, as reliable stillbirth data is scarce. This leads to a modest underestimation in the annual affected births calculated (26).

Anecdotal evidence suggests a higher incidence of consanguinity in specific regions, but the lack of available empiric data required a uniform consanguinity adjustment to be applied to the IMR across all provinces. This may lead to an overestimate of adverse outcomes for consanguinity associated disorders.

Data Collated for input

Specific data required are listed in Table 1. Where demographic data were not available for the smallest civil division e.g. district, the next level up (provincial or national) was sourced.

[5] Neurological damage leading to cerebral palsy may occur in utero, at birth, or later e.g. due to meningitis or subaponeurotic/subgaleal haemorrhage.

Data sources

Optimal sources of data were identified following careful consideration (see Table 1), due to the relationship between the quality of the demographic data used and quality of the estimates derived.

Table 1. Details of demographic data indicators required and sourced. Unless otherwise specified, each indicator was used in all MGDb-ZA calculations.

Indicator	Data source	Civil Division	National Total or Rate
Population (1 000s)	CARe projection model[6]	Provincial	52 261
Annual (live) births (1 000s)	CARe projection model[5]	Provincial	1 169
Infant mortality rate	CARe projection model[5]	Provincial	28/1 000 LB
Under-5 mortality rate	CARe projection model[5]	Provincial	46/1 000 LB
Mean life expectancy	CARe projection model[5]	Provincial	62 (male & female)
Total fertility rate	Dorrington & Moultrie 2015 (30)	Provincial	2.5
Sex ratio at birth	CARe projection model[5]	Provincial	1.02
Stillbirth rate	Cousens *et al* 2011 (31)	National	20.4 /1 000 births
Neonatal mortality rate	40% IMR[5]	Provincial	11.3/ 1 000 LB
Crude birth rate	CARe projection model[5]	Provincial	21.9
Percentage urbanized	CARe projection model[5]	Provincial	63%
Percentage mothers aged 35+[7]	CARe projection model[5]	Provincial	13%
Coefficient of consanguinity (F)[8]	Modell *et al* 2016 (26)	National	0.007
IMR adjusted for HIV/AIDS [7]	Johnson *et al* 2016 (32)	Provincial	25
IMR adjusted for HIV/AIDS and consanguinity	Modell *et al* 2016 (26) & Johnson *et al* 2016 (32)	Provincial/ National	24

Data adjustment for estimating access

In the MGDb, access to care refers to access to the typical range of services available when the IMR is 10 per 1 000 live births or lower (26). The IMR is the basis of the formula used to estimate access to care and was adjusted for the effect of the HIV/AIDS epidemic and for parental consanguinity, due to their disproportionate contribution to infant mortality in SA compared to other populations (26). Provincial IMRs, excluding HIV/AIDS

[6] Professor Rob Dorrington, Centre for Actuarial Research, University of Cape Town, Personal Communication.

[7] Percentage of mothers aged 35+ is required for calculating estimates for chromosomal disorders.

[8] Coefficient of consanguinity and HIV/AIDS related mortality are required to adjust the IMR for use in the calculation of access to service.

deaths, were sourced (32), and a further 1.4 infant deaths per 1 000 live births (based on coefficient of consanguinity) deducted from the IMR to adjust for consanguinity (26).

Data Analysis

The MGDb-ZA was adapted from a model of the MGDb as provided on 30 August 2016 in a series of Microsoft Excel spreadsheets. Integrated formulae based on birth prevalence data updated automatically when South African demographic data was inputted. Formulae, data sources, birth prevalence and other rates, and methodologies used in the MGDb are detailed in Epidemiological Methods in Community Genetics and the Modell Global Database of Congenital Disorders (MGDb) available online (26).

The MGDb-ZA generated a set of four outputs for 2012:

1. ***Baseline birth prevalence and birth outcomes in the absence of any care/intervention.*** This provides a baseline to quantify the scale of the problem and against which to evaluate the impact of current interventions.
2. ***Birth outcomes with access to available care/interventions.*** This includes effects of pre-conception and pre-natal interventions including folate fortification, prenatal diagnosis (PND), genetic counselling, termination of pregnancy (TOP) and diagnosis/care from birth.
3. ***Disorder-specific survival and disability:***
    a. In a baseline no-care situation
    b. With optimal care (IMR estimate of access to care)
4. ***Obtaining country-specific estimates:*** Calculated from the proportion of the population estimated to have no access to care and access to optimal care

Key findings of the MGDb-SA are presented below.

Results

Collated Data for input

The demographic data collated is summarised in Table 1. Nationally, just under a third (30%) of the population was estimated to have access to optimal services.

Baseline outcomes in the absence of intervention

Table 2 summarizes the baseline birth outcomes *without* intervention. Total birth prevalence for all groups of CDs was estimated at 30.5 per 1 000 live births. Of the total live births affected, a quarter died during the first month of life (n=9 535) and half (n=16 855) under-5. Most live births affected by NTDS (94%, n=995), autosomal dominant single gene disorders (97%, n=1 585) and other trisomies (99%, n=385) died under-5, with over 85% of NTD (n=880) and other trisomy deaths (n=335) occurring during the

first month of life. A high proportion (over 90%) of survivors at age 5 was seen for sex chromosomal disorders (Turner and Klinefelter syndromes), oculocutaneous albinism and usually less severe malformations.

Birth outcomes with access to care

Birth outcomes *with* access to care are detailed in Table 3. Compared to baseline outcomes, an estimated 1 860 affected births were avoided through pre-conception and pre-natal interventions (folate fortification, PND, genetic counselling and TOP). The birth prevalence was reduced by 1.1 per 1 000 live births resulting in 225 fewer stillbirths and 1 635 fewer affected live births. Overall access to care resulted in just under a third (30% n=10 320) of total live births receiving care and almost two-thirds (n=23 585) receiving no care. Overall survival increased by 12% (n=3 235) at 5 years of age with care compared with baseline estimates. A reciprocal decrease was seen in deaths from CDs, with 37% (n=12 665) dying under-5 compared with 50% (n=17 675) without care (baseline). Deaths from other causes under-5 increased by 140. The proportion of under-5 deaths occurring during the neonate period remained at just over 50% (3% decrease). The overall proportion of affected stillbirths remained the same. Comparative results for each of the specific disorder groups are detailed in separate sections below.

Single Gene Disorders

The birth prevalence of single gene disorders represented just over a quarter of the total CD groups modelled, with consanguinity-related recessives accounting for the greatest proportion. Access to care for single gene disorders was 31% (n=2 960). Birth prevalence decreased with access to care by 0.3 per 1 000 live births due to a 0.2 reduction for recessive disorders and minimal reductions for consanguinity related recessives and genetic type unknown.

Some 305 affected births were avoided by pre-conception and pre-natal intervention. The number of live births with baseline recessive disorders decreased by 245, contributing the bulk of the 3% reduction in single gene disorders affected.

Affected stillbirths were estimated to account for 11% (n=210) of baseline recessive disorders and 17% (n=790) of consanguinity-related affected births, with access to care making a minimal difference.

Table 2. MGDb-ZA baseline birth prevalence and estimated outcomes for 2012 with no intervention (rounded to nearest multiple of 5).

	Birth Prevalence per 1 000 LB	Affected Stillbirths	Affected Live Births	Neonatal Deaths (<28 days)	Infant Deaths (< 1 year)	Under-5 Deaths	Deaths (other causes)	Survivors at 5 years
Single Gene Disorders								
Autosomal Dominant	1.4	0	1 635	300	960	1 585	50	0
X-Linked	0.1	0	60	10	20	25	0	35
Baseline Recessive	1.7	215	1 940	430	760	945	70	925
Genetic Type Unknown	1.2	0	1 355	260	465	530	50	775
Oculocutaneous Albinism	0.3	0	290	0	0	0	15	275
Recessive Increment/consanguinity	3.9	800	4 520	1 000	1 775	2 205	160	2 155
Total Single Gene Disorders	**8.4**	**1 015**	**9 800**	**2 000**	**3 980**	**5 290**	**345**	**4 165**
Chromosomal Disorders								
Down Syndrome	1.7	100	2 010	705	900	1 370	45	595
Other Trisomies	0.3	475	390	335	385	385	5	0
Rare Autosomal	0.6	180	645	245	300	465	35	145
Turner Syndrome	0.2	55	205	0	0	0	10	195
Klinefelter Syndrome	0.7	20	820	0	0	5	35	780
Total Chromosomal Disorders	**3.5**	**830**	**4 070**	**1 285**	**1 585**	**2 225**	**130**	**1 715**
Malformations								
Congenital Heart Disease[3]	3.6	60	4 260	1 580	2 725	2 815	105	1 340
Neural Tube Defects	0.9	295	1 060	880	970	995	0	65
Oral Facial Clefts	0.2	5	280	90	180	225	5	50
Very Severe Other Malformations	7.6	260	8 900	3 610	4 325	4 890	245	3 765
Less Severe Other Malformations	5.2	40	6 020	40	90	270	270	5 480
Total Malformations	**17.5**	**660**	**20 520**	**6 200**	**8 290**	**9 195**	**625**	**10 700**
Additional Conditions								
Thyroid a/dysgenesis	0.1	0	115	0	30	60	5	50
Prem Associated PDA	0.3	0	350	50	105	110	15	225
Pyloric Stenosis	0.7	0	820	0	795	795	25	0
Total Additional Conditions	**1.1**	**0**	**1285**	**50**	**930**	**965**	**45**	**275**
Total	**30.5**	**2 505**	**35 675**	**9 535**	**14 785**	**17 675**	**1 145**	**16 855**

With access to care, 6% (n=445) more live births with single gene disorders survived at 5 years than in baseline estimates, with a reciprocal decrease in deaths under-5 (n=5010). This included 245 surviving with autosomal dominant conditions compared to none without intervention. Survival at 5 years of births affected by oculocutaneous albinism remained unchanged; survival increased by almost 10% (n=5) for x-linked disorders and by 5% or less each for genetic type unknown (n=50), baseline recessive disorders (n=40) and consanguinity-related (n=185).

Chromosomal Disorders

Chromosomal disorders accounted for 14% (n=4 900) of overall affected births, with Down syndrome contributing half, with minimal changes following intervention. Access to care for chromosomal disorders averaged at 25% due to only 14% of Klinefelter syndrome being diagnosed even when there is optimal care available (26).

A total of 265 affected births were avoided through pre-conception and pre-natal intervention, specifically PND and genetic counselling. Overall, 80 fewer stillbirths and 180 fewer livebirths were affected, including 13% less other trisomies (n=110), 11% (n=30) less Turner syndrome and 8% (n=65) less births affected by rare autosomal disorders. Of the total births affected, over half of those with other trisomies, a fifth with rare autosomal disorders, a further fifth with Turner syndrome and 5% with Down syndrome were stillborn. These proportions remained unchanged with access to care.

Survival at 5 years of age rose overall for chromosomal disorders by 11% (n=335) with access to care, with survivors of rare autosomal disorders and Down syndrome each increasing by approximately 15% (n=90 and n=275 respectively). Most live births affected by sex chromosomal disorders (Klinefelter and Turner syndromes) survived to the age of 5, while none affected by other trisomies survived, and this remained unchanged with access to care.

Overall, 500 fewer deaths under-5 occurred with access to treatment for births affected by chromosomal disorders. More than half of these deaths (n=280) were prevented as neonates, with mortality during the first month of life dropping from a third of affected births to a quarter. A 10% reduction in neonatal deaths was seen both for Down syndrome (n=190) and rare autosomal disorders (n=75). Infants affected by other trisomies all died within the first year of life with or without intervention, surprisingly, the proportion of deaths during the neonatal period increased by 9% with access to care.

Table 3. MGDb-ZA estimated birth outcomes for 2012 incorporating access to available care (rounded to nearest multiple of 5).

	Birth Prevalence per 1 000 LB	Affected Births Avoided	Affected Stillbirths	Affected Live Births	Diagnosis & Care	No Diagnosis or Care	Neonatal Deaths (<28 days)	Infant Deaths (<1 year)	Under-5 Deaths	Deaths other causes	Survivors at 5 years
Single Gene Disorders											
Autosomal Dominant	1.4	0	0	1 635	510	1 130	225	830	1 340	50	245
X-Linked	0.1	0	0	60	20	40	5	20	20	0	40
Baseline Recessive	1.5	245	210	1 700	530	1 170	305	615	750	65	885
Genetic Type Unknown	1.1	20	0	1 335	415	920	200	395	460	50	825
Oculocutaneous Albinism	0.3	0	0	290	90	200	0	0	0	15	275
Recessive Increment/consanguinity	3.8	40	790	4 485	1 395	3 090	810	1 620	1 985	160	2 340
Total Single Gene Disorders	**8.1**	**305**	**1 000**	**9 505**	**2 960**	**6 550**	**1 545**	**3 480**	**4 555**	**340**	**4 610**
Chromosomal Disorders											
Down Syndrome	1.7	60	100	1 955	610	1 345	515	700	1 035	50	870
Other Trisomies	0.3	110	415	340	105	235	320	340	340	0	0
Rare Autosomal	0.5	65	165	595	185	410	170	235	345	15	235
Turner Syndrome	0.2	30	50	180	55	125	0	0	0	10	170
Klinefelter Syndrome	0.7	0	20	820	35	785	0	0	5	40	775
Total Chromosomal Disorders	**3.3**	**265**	**750**	**3 890**	**990**	**2 900**	**1 005**	**1 275**	**1 725**	**115**	**2 050**
Malformations[9]											
Congenital Heart Disease[3]	3.3	350	55	3 915	1 215	2 700	700	1 175	1 215	150	2 550
Neural Tube Defects	0.6	505	185	665	165	370	325	350	390	140	135
Oral Facial Clefts	0.2	15	5	255	80	175	55	110	140	5	110
Very Severe Other Malformations	7.5	385	245	8 535	2 650	5 880	2 750	3 320	3 730	240	4 565
Less Severe Other Malformations	5.2	35	40	5 990	1 860	4 125	60	95	225	270	5 495
Total Malformations	**16.9**	**1 290**	**530**	**19 360**	**5 970**	**13 250**	**3 890**	**5 050**	**5 700**	**805**	**12 855**
Additional Conditions											
Thyroid a/dysgenesis	0.1	0	0	115	35	80	0	20	45	0	70
Prem Associated PDA	0.3	0	0	350	110	240	35	70	75	15	260
Pyloric Stenosis	0.7	0	0	820	255	565	0	555	565	10	245
Total Additional Conditions	**1.1**	**0**	**0**	1 285	400	885	35	645	685	25	575
Total	**29.4**	**1 860**	**2 280**	**34 040**	**10 320**	**23 585**	**6 475**	**10 450**	**12 665**	**1 285**	**20 090**

Malformations

Non-chromosomal isolated malformations accounted for the majority of the total CDs modelled in this study, contributing over 50% of affected births in baseline estimates (n=21 180) and with access to care (n=19 890). Access to care for malformations was 31%. Birth prevalence for malformations decreased by 0.67 following pre-conception and pre-natal intervention, with CHDs (0.30) and NTDs (0.34) accounting for the bulk of this drop. CHDs accounted for a fifth of all malformations, with potentially very severe other malformations (consisting of seven sub-groups of very severe malformations), collectively accounting for over 40% of malformation birth prevalence and less severe malformations for just under a third.

A total of 1290 affected births were avoided through pre-conception and pre-natal interventions, including 39% (n=505) NTD affected births and just under a third each of CHDs (n=350) and very severe other malformations (n=385). Following intervention, a total of 130 fewer stillbirths and 1160 fewer live births were affected by malformations in comparison to baseline estimates, although overall proportional amounts remained similar for each category. The number of livebirths affected by NTDs decreased by 395 with access to pre-conception, pre-natal intervention and care following birth. Affected livebirths for CHDs and OFCs also decreased by 345 and 25 respectively, following intervention.

Intervention increased survival of births affected by malformations by 14% (n=2155). The greatest increase was seen for CHDs, with a third more surviving (n=1210), followed by OFCs with a quarter more (n=60), NTDs (14% n=70) and potentially very severe malformations (11% n=800). Usually less severe malformations accounted for the most survivors (>90%) at 5 years, both for baseline estimates and with care.

With intervention, 15% (n=3495) fewer births affected by malformations died under the age of 5, excluding deaths from other causes. This included a third fewer deaths each from CHDs, NTDs, and OFCs.

Additional Conditions

The birth prevalence for additional conditions accounts for only 3.6% of total CDs modelled, and remained unchanged with access to care. No births were avoided through pre-conception or pre-natal care, with the number of affected livebirths and zero stillbirths remaining the same. Access to care for additional conditions was 31%.

Baseline estimates indicated only 21% (n=275) of affected births survived to the age of 5, excluding pyloric stenosis cases, which were all estimated to have died under-5. With

care, survival at 5 years doubled (n=575), including a third surviving (n= 245) for pyloric stenosis whereas none survived previously.

Under-5 deaths from additional conditions decreased by 22% (n=280) with access to care. With access to care only those affected by prematurity associated PDA resulted in neonatal deaths, which decreased by 5% (n=15).

Disorder-specific survival and disability (Baseline & with care)

Proportional changes in disability and survival with access to care are detailed in Table 4. With access to care an overall reduction of 5% (n=100 598) in years affected was seen, 13% less years of life were lost and a slight increase in years lived with disability. As the result of intervention, 12% of years affected were lived cured. The number of years affected per person of the total birth cohort decreased by 0.08 to 1.81 with access to care. No years lived cured resulted from access to care for single gene or chromosomal disorders.

Discussion

This study modelled birth outcomes for four categories of CDs in SA to supplement the current lack of empiric, observed data. Collated SA demographic data was used to adapt the MGDb to develop national birth prevalence and birth outcomes (live births, stillbirths, under-5 deaths, survival at 5 years) for specific early onset, endogenous CDs. This was undertaken for 2012, initially in the absence of any intervention to provide baseline estimates to indicate the scale of the problem.

An important upfront consideration is the diversity in data sources utilised by the MGDb method which affects the reliability of the modelled estimates. The principle reference sources used for the baseline prevalence estimates in the MGDb are strongly evidence-based and are conservative estimates to prevent overestimation (26). The evidence basis for the calculation of outcome estimates is less robust. While there is observed evidence for the impact of folic acid (26) (33), access to PND and TOP are estimates only. Similarly, survival data for chromosomal disorders and some malformations is reliable, but is outdated for CHDs and may lead to an overestimation of CHD-related early mortality and an under-estimation of disability (26, 34).

The portion of the population with access to optimal care was calculated using the IMR and applied to the same dataset enabling birth outcomes with access. Optimal care is defined in the MGDb as the level of care typically available when infant mortality is 10 per 1 000 live births or lower, although in principle it should include all interventions available at the relevant time (26). Survival and disability outcomes were also estimated to compare the impact of access to care.

Table 4. MGDb-ZA disorder-specific proportional changes in survival and disability for South Africa in 2012.

	Outcomes, % of years affected per person									
	No care (Baseline) outcomes				Estimated outcomes with care					
	Potential Years Life Affected	Potential Years affected/person	Potential Years Life Lost	Potential Years Lived with Disability	Actual Years affected	Reduction in Years affected	Actual Years affected/person	Actual Years Life Lost	Actual Years Lived with Disability	Actual Years Lived Cured
Single Gene Disorders	607 742	0.52	90%	10%	589 179	3%	0.50	82%	18%	0%
Chromosomal Disorders	252 272	0.22	66%	34%	241 070	4%	0.21	64%	36%	0%
Malformations (Non-syndromic Isolated)	1 271 417	1.09	66%	34%	1 200 326	6%	1.03	48%	32%	20%
Additional Conditions	79 675	0.07	88%	12%	79 934	0%	0.07	62%	13%	25%
Total	**2 211 106**	**1.89**	**73%**	**27%**	**2 110 508**	**5%**	**1.81**	**60%**	**28%**	**12%**

The scale of the burden of CDs from the baseline estimates, indicates that without care, more than half of affected births die before 5 years of age. The 30% access to care has a substantial impact, preventing 5 010 of these early deaths and avoiding a further 1 860 through pre-conception and pre-natal intervention. With half of under-5 deaths occurring during the neonatal period with or without care, improved access to optimal care, including early diagnosis and treatment, may potentially prevent more deaths during this high-risk period.

Single Gene Disorders

The low proportion of affected single gene disorder births that are avoided with access to care (n=305), is an indication of the lack of available screening as part of routine antenatal care. There is no mandatory national newborn screening programme in SA and such tests are only available in the private sector, with limited carrier screening available in some public health sector laboratories (17). The majority of births avoided are for baseline recessive and consanguinity related disorders such as thalassemia, sickle cell anaemia, cystic fibrosis, Gaucher disease and others, which predominate in SA (35). Many of these conditions are treatable, enhancing survival for affected births following diagnosis.

The modelled estimates confirm that recessive disorders are present at a higher rate in births resulting from consanguineous unions, and the rarer the allele the greater the relative risk (36). The full potential of genetic counselling in educating families on potential risks to enable informed decision making regarding reproductive choices and PND remains constrained due to severely curtailed capacity (37) and is less immediately visible in a country with a low total fertility rate such as SA. Anecdotal evidence suggests consanguinity to be more common in specific population groups in Limpopo and North West Provinces (Arnold Christianson, personal communication). Due to limited availability of local data on the prevalence of parental consanguinity, a uniform consanguinity adjustment was used in the MGDb-ZA in the calculation of estimates. Improved data is required to better estimate nuances in the impact of this practice relevant for the development of services.

Early-onset dominant autosomal conditions have a lower birth prevalence than recessive disorders. They are less likely to receive an early diagnosis and appropriate care due to limited facilities and lack of skilled clinicians (10, 15, 16). Owing to the aetiology of single gene disorders, curative interventions[9] are not currently possible.

[9] Curative interventions refer to treatments or surgeries that effectively 'cure' the disorder, i.e. enable the affected person to live a normal life with no additional medical surveillance or intervention – e.g. curative paediatric surgery. Where genetic disorders

No impact is seen for access to care for those affected by oculocutaneous albinism in children under-5 as this condition is not life threatening in itself. However, skin cancer is a major cause of death and shortens the life-span for those affected, making preventative treatment from an early age vital, including UV-protective clothing, sunscreen, encouraging an indoor lifestyle and early presentation of skin cancers (38).

Chromosomal Disorders

The impact of PND and genetic counselling as part of pre-conception and pre-natal intervention was minimal, with 265 chromosomal affected births avoided. With the rate of Down syndrome and other trisomies strongly related to maternal age, ultrasonography and amniocentesis services should be offered routinely for all expectant mothers over the age of 35. A scan, invasive testing and accompanying genetic counselling are recommended by the 2015 Guidelines for Maternity Care (39), but cannot occur routinely (40, 41) due a lack of infrastructure and skilled capacity (42). Despite being freely available in limited locations since 1994, the current system fails to deliver comprehensive ante-natal care for mothers of advanced maternal age, with frequent missed referral opportunities and the option of PND often withheld (40).

This modelling exercise has demonstrated that early diagnosis and access to care can substantially improve survival. When a third of the population have access to optimal care, an additional 15% of those affected by Down syndrome survive to age 5, with similar outcomes for rare autosomal disorders. Diagnosis of Down syndrome after birth continues to be a challenge in SA, preventing early access to life-saving care, genetic counselling and rehabilitation to ameliorate disability, reducing survival rates (41). Many of those affected by Down syndrome continue to die undiagnosed, compounded by the lack of cardiac surgery available (41, 43, 44), and their deaths are recorded under other NCD-10 codes (41).

With no survivors at 5-years for other trisomies, these life-limiting conditions often result in the withdrawal of treatment and implementation of palliative care only (45). The unexpected finding of a greater proportion of other trisomies dying during the prenatal period *with* access to care than for baseline estimates warrants further investigation. Improved services may increase survival at all stages other than for neonates, while Janvier *et al* (46) suggest that a later diagnosis confers a 'survival advantage' since full care is given up until the point of diagnosis. A more likely explanation in the context of this study may be an unresolved calculation error.

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are concerned, treatment may ameliorate the disorder but at present rarely leads to effective cure.

The less pronounced impact of care for sex chromosomal disorders is because this study is focused on survival and these conditions are not life limiting. Only a small portion of affected males with Klinefelter syndrome are diagnosed, usually after puberty due to associated health issues (47, 48). Health issues are more severe for females affected by Turner syndrome and may reduce life expectancy (49). For both these sex chromosomal disorders, access to care has more impact on the quality of life experienced by those affected, than on the quantity.

Malformations

The greatest impact of access to care was seen in this category of CDs which contribute over 50% of the overall birth prevalence in the study.

The MGDb includes non-chromosomal isolated early onset congenital heart disease caused by congenital heart defects (CHDs) that cause death or disease before the age of 20 (26). CHDs account for a fifth of the malformations group and are the most common CD at birth. The lack of PND results in a low rate of TOP even for severe CHDs. Diagnosis after birth is also challenging for these unseen CDs, requiring examination by a skilled clinician which does not occur routinely before discharge of newborns in SA or for home births. Accurate diagnosis may be assisted by pulse oximetry pre-discharge screening, which is not routinely available in SA but has proven feasible (50).

Folate fortification reduced CHD affected live births by 8%, accounting for the majority of 350 avoided CHD affected births following access to care. The high birth prevalence of CHDs results in a large number of unaffected births. The increased survival of affected births of just over a third may be largely attributed to corrective cardiac surgery. Although historically paediatric surgery has been perceived as prohibitively expensive and of little relevance for MLICs (51, 52), evidence is emerging to the contrary (51, 53, 54). A fresh approach integrating corrective surgery into health care policy and systems rather than as vertical programmes and developing local paediatric surgical expertise and the required infrastructure, could place paediatric surgery at the forefront of reducing avertable suffering in children, and offer considerable socioeconomic benefits.

The majority of births avoided for NTDs is attributed to the folate fortification of staple foods in SA (maize meal and bread) implemented since 2003. The 31% reduction in NTDs reported by Sayed *et al* (33) was the basis for the calculation in the MGDb-ZA, causing the reduction in birth prevalence by 0.3 per 1 000 live births. An additional small percentage of prenatally diagnosed NTDs were medically terminated. It must be noted that anencephaly contributed a fifth of the live births affected by NTDs, but all die shortly after birth regardless of access to care. Folate fortification also reduces OFC affected births but to a lesser extent due to the lower baseline birth prevalence (33).

The substantial increase in survival with malformations with access to care is largely due to surgical intervention as outlined above. In the case of potentially lethal conditions such as cleft lip/palate, it can offer an effective cure and ameliorate the degree of disability (10). Of the 70% of CDs that can be cured, prevented or have their associated disability ameliorated (55), the 40% that can be cured or largely ameliorated are mostly malformations tackled primarily by means of surgical intervention (15). This highlights the need to invest more into developing surgical capacity in SA, where it could substantially increase survival and function for children with malformations.

Additional Conditions

The additional conditions included in this study serve largely as placeholders for more to be added in the future. For example, the value of therapeutic treatment and intervention after birth is particularly emphasised by the reduction by one third in under-5 deaths from congenital hypothyroidism, and the increase in survival following surgery for pyloric stenosis. This eclectic group of conditions highlights the tailored care approach required for each specific disorder that, when applied, can yield optimal results.

Survival and disability

The years lived cured and lives saved through access to care dispels the widely-held myth that 'little can be done to treat CDs'. With the increase in survival (excluding those cured through surgery) comes a greater proportion living with disability resulting from CDs requiring therapeutic treatment -emphasizing the increased commitment, capacity and resource allocation needed for their care. Rehabilitation, including neurodevelopmental, speech, and occupational therapies to ameliorate the degree of disability and enhance quality of life needs to be accompanied by appropriate psychosocial support (10). Care of those affected by CDs should be balanced with prevention to ensure sustainability of care services (10).

Limitations

The use of provincial estimates for IMR, U5MR and neonatal mortality rate was necessary due to the incompleteness of vital registration data at the district level. Although registration completeness has improved over the past two decades with legislation (56, 57) making it compulsory, low levels of completeness persist for children under-5 years, especially for infants (58-61). Data for 1992-2014 from the Agincourt Health and Socio-Demographic Surveillance System reported death registration for children under-5 at only 33.7% and infants at 26.7% (59). Most deaths of rural children with serious CDs occur outside health facilities with traditional burial occurring at home. Mothers cannot afford the expense and time away from home and work to take these

children to hospital to die (62). (Professor Arnold Christianson, personal communication). This also contributes to underreporting of CDs since many of these unregistered deaths may be undiagnosed CDs.

The development of the MGDb-ZA was instrumental in highlighting areas for improvement of the MGDb, and refining the modelling methods utilised as part of its ongoing evolution.

The findings of this study have quantified the baseline scale of the burden of specific early onset endogenous CDs in SA for 2012. Modelled estimates for access to 30% available care demonstrated the proportional change in birth outcomes made possible by care – reducing birth prevalence, decreasing mortality, providing curative interventions and therapies, and ameliorating disability for the increasing number surviving. If improved services were more widely available, an even greater proportion of lives could be saved or be qualitatively improved.

This study indicates the number of lives affected by CDs is much higher than the number documented by national CD surveillance (21). Current capacity is inadequate to accurately diagnose, refer and care for those affected by CDs. With over 40% of under-5 deaths occurring during the neonatal period in SA (63), more needs to be done during this critical period of early life. Early diagnosis and appropriate care could help reduce these deaths, many of which are preventable, and could contribute towards achieving the Sustainable Development Goal 3 target of an U5MR of 25 per 1 000 live births by 2030 (64).

Currently capacity is lacking in the medical genetics services sector (8) and political commitment and accompanying resources are required if the situation is to improve. Without this increased capacity, the necessary primary, secondary and tertiary prevention and care of CDs cannot be effectively implemented for the wellbeing of those affected in SA.

Conclusion

This study has highlighted the importance of empiric data on CDs in SA. It is hoped that the findings of this study will stimulate policy makers to initiate informed development and universally accessible implementation of cogent medical genetic services, particularly in primary healthcare (PHC) including improved surveillance of CDs. Areas for further study include in-depth analyses of modelled estimates (a) for specific CDs and (b) in specific provinces of SA, and costing of specific interventions for their care and prevention.

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Part Four: Building capacity

Part Four focuses on the need to increase capacity in the medical genetics sector in SA. The regression in these services is bringing the country to a crisis point as the health need of CDs continues to increase. The article which makes up Chapter 9 briefly outlines the situation in the country, as covered in Part One of this study and explains the history of medical genetic services and capacity development. Reasons for the decline in capacity are outlined and the challenges in building the required capacity quickly. The role of the genetic nurse is highlighted as the potential cornerstone of the sector, and as a means to quickly regenerate the required services.

Two existing tools are profiled to potentially develop the large numbers needed in a short space of time. Collectively, the Medical Genetics Education Programme (MGEP) and the Congenital Disorders Course Book could be used to build up a nursing workforce with improved knowledge and skills in medical genetics. If implemented within the relevant primary healthcare streams of the National Health Insurance (NHI) scheme (1), this could help CDs being prioritized as a health care issue in the country.

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Chapter 9: The case for the genetic nurse in South Africa

This article has been submitted to the Journal of Community Genetics.

Malherbe HL, Christianson AL, Woods D, Aldous C. The case for the genetic nurse in South Africa. Journal of Community Genetics (under review).

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Acknowledgements:
This research was supported by a bursary via the College of Health Sciences, University of KwaZulu Natal. Inputs from Sarah Walters, Genetic Counsellor are appreciated.

Abstract

The care and prevention of congenital disorders (CDs) is an emerging, but unprioritised health need in South Africa (SA). Inadequate empirical data and underreporting conceals the true burden of CDs while medical genetic services to confront the problem have regressed. Positive epidemiological transition in the country now demands these services are improved to significantly further reduce child mortality. Current sector capacity in SA is inadequate and required personnel targets will not be reached quickly enough to meet the growing health need even if relevant posts are designated. Historically, genetic trained nurses played a defined role in primary health care (PHC) by recognizing and diagnosing common CDs and counselling patients and their families, whilst referring complex matters to the limited tertiary medical genetic services available. Policy changes to redress past inequalities and other healthcare priorities resulted in genetic services being incorporated into PHC, with few genetic nurses retaining their genetic services role. While the medium to long term aim for SA would be to develop medical genetic services with appropriate capacity at all levels of healthcare, there is an urgent short term need to provide basic medical genetic services in PHC. Central to achieving this is the up-grading and re-implementation of the previously successful Medical Genetics Education Programme (MGEP). This post-graduate distance learning, education programme is implemented with the Congenital Disorders course book, a distance education tool promoting independent, home-based learning. Together, these tools offer an approach to swiftly build up a nursing workforce with improved knowledge and skills in medical genetics.

Keywords: congenital disorders, genetic nurses, South Africa, medical genetics education programme, education and training.

Introduction

Congenital disorders (CDs) are a common, costly and critical health issue. Defined as abnormalities of structure or function present from birth, this includes all disorders caused by environmental, genetic and unknown factors, whether evident at birth or manifesting later in life (1). In South Africa (SA), it is estimated that CDs affect 6.8% or one in 15 live births (2). As for many middle and low income countries (MLIC), the true contribution of CDs to the disease burden is significantly underestimated in SA, with national surveillance underreporting CDs by 98% (3). Many remain undiagnosed or are misdiagnosed and the cause of death wrongly attributed (4-6). This is largely due to the lack of skilled clinicians to identify and diagnose CDs, combined with inadequate facilities (4, 5, 7).

As for many MLIC, Millennium Development Goal 4 to reduce child mortality by two thirds by 2015 was not reached in SA. However, rapid reductions were achieved until 2011 (8, 9). Various interventions, including HIV/AIDS programmes and the Expanded Programme of Immunization, have contributed to bringing the country back into positive epidemiological transition (10-12). As SA develops and communicable diseases are better controlled, the proportion of child deaths and disability resulting from CDs is rising (2, 13). This follows the trend of high income countries, where CDs emerged in the 1960's and remain as the leading cause of death in children, accounting for up to 28% of deaths in the under-fives (2, 7, 14-16).

Despite the lack of empirical data in SA, the previously hidden disease burden of CDs is beginning to emerge through mortality data (11). In 2013, congenital abnormalities (a sub-set of CDs) overtook infection as the third leading cause of death in early neonates (17). As reported by Malherbe *et al* in 2016, this trend in early neonatal deaths continued in the Western Cape (WC) in 2014, a province which serves as a healthcare proxy for other provinces in the future (11).

With the stagnation of the SA infant mortality rate (IMR) and under-5 mortality rate (U5MR) since 2011 and neonatal mortality rate since 2009, efforts are underway to further reduce child deaths in SA (8, 11, 18). While these interventions will save child lives, none confront the health issue of CDs - limiting the IMR from being significantly further reduced. One example is the 9 469 newborn and child lives potentially saved annually by scaling up 11 specific interventions (18). These are overshadowed by the 47 120[1] lives that could be saved and/or disability ameliorated every year by implementing

[1] Based on 2014 live births of 1 242 070 (Statistics South Africa. Mid-year population estimates 2015. Statistics South Africa, Pretoria) and a prevalence rate of 54.2 (7).

appropriate care and prevention for 70% of genetically determined CDs alone (19).[2] Currently, one of the only primary prevention interventions comprehensively implemented countrywide in SA is the fortification of maize meal and wheat flour with folic acid, which has resulted in a 30% reduction in neural tube defects since its introduction in 2003 (20).

CDs have not yet been addressed in SA as a priority health care issue in terms of World Health Resolution (WHA) 63.17 of 2010 (21), which outlined specific actions for commitment and allocation of resources by member states. Implementing comprehensive services for the care and prevention of CDs usually begins when a country's IMR is between 40-50 deaths per 1000 live births (22, 23). Despite an IMR of 28 per 1000 live births in 2015 (8), SA is yet to comprehensively implement genetic services in SA. Such services could be key in significantly reducing child mortality further (11). While competing health priorities are contributing factors for this lack of prioritisation of CDs, it is now essential that medical genetic services are implemented for this crucial category of non-communicable disease (24).

Medical Genetic Services

Medical genetic services improve health by preventing CDs and reduce suffering by offering care to those affected (7). The key to reducing the contribution of CDs to the burden of disease, is to offer the 'best possible patient care in the prevailing circumstances', and prevention so that people affected by or at risk of having children with CDs 'can live and reproduce as normally as possible' (4, 22, 25).

The completion of the Human Genome Project in 2003 highlighted the genetic component of disease, triggering advanced research with many new genetic screening and diagnostic tests becoming available (26). As a result, medical genetics is becoming a field of relevance to the healthcare of many (27). Genetic services are required across the continuum of care, but initially focus upon reducing child mortality. As countries transition epidemiologically, the role of genetic services widens to encompass complex multifactorial conditions (of later onset). In SA, the quadruple burden[3] of disease and non-classical epidemiology are impeding CDs from being recognized as significant causes of mortality and morbidity. CDs are the portfolio of the Women's Health and Genetics Directorate under the Women's Maternal and Reproductive Health cluster at

[2] Excluding lives affected by teratogens that could be potentially saved, which account for almost 20% of CDs in SA (2).

[3] The quadruple burden of disease in SA includes HIV/Aids and TB; violence and injuries; high maternal and child mortality; and non-communicable diseases.

the National Department of Health (NDoH). CDs are currently excluded from non-communicable disease (NCD) strategies nationally, negatively impacting their care and prevention.

The lack of capacity

A key barrier to the development of medical genetic services globally is a lack of capacity, impacting industrialised and developing countries alike, albeit on a different scale of magnitude (26). Although inadequate capacity is a widespread constraint in SA throughout healthcare, the impact of these staff shortages in medical genetic services is disproportionately inhibitive on healthcare development given the epidemiology of CDs. In SA, comprehensive medical genetic services are currently only available at four academic centres[4], which excludes six of the nine provinces from accessing such services, other than via limited outreach clinics in some areas. Even within the provinces where genetic services are available, access and service vary according to geographical location, and outreach clinics are necessary to penetrate rural areas. Only 11 medical geneticists are practicing full-time countrywide (one per 5 million of the population), and less than eight genetic counsellors are practicing in the state sector (one per 7.3 million) (11) (Shelley McCaulay Personal Communication 12 August 2016). Laboratory testing facilities and capacity are also severely compromised.

This capacity falls far short of national recommendations of 27 medical geneticists (1 per 2 million) and 95 genetic counsellors (1 per 580 000) required today to provide a basic universal service (28). Until recognition as a primary medical specialty in 2007, medical genetics was a sub-specialty under which many registered under a grandfather clause in 1999 (29). Although 17 medical geneticists have qualified since 2001 and six registrars are currently in training, this additional capacity has been offset by a loss of 19 to the sector. Seven have retired, six have emigrated, two have died, two moved to private practice and two are not currently practicing. Genetic counsellor numbers are similarly limited with many of those qualifying remaining unavailable to public service as posts have been closed or frozen, forcing their emigration, move to other fields or the private sector, where seven are currently practising.

With limited posts available and few doctors choosing to specialise in medical genetics within the greater context of a doctor shortage in SA,[5] it is unlikely that capacity targets

[4] Comprehensive genetic services are available at the University of Cape Town, University of the Free State, University of Stellenbosch, University of the Witwatersrand.

[5] 60 doctors per 100 000/population in 2013 compared to the global average of 152/100 000 (ECONEX. Identifying the determinants of and solutions to the shortage

will be reached in the medium term. With only four training centres available to train medical geneticists countrywide[6], and only two centres[7] training genetic counsellors and a severe shortage of allocated posts, these circumstances necessitate other options to be considered for the more immediate expansion of services. This speaks to the role of allied healthcare professions, specifically nurses, who can undertake a key supplementary role in genetic services.

History of genetic nurses in South Africa

While the potential role of nurses in genetic services is not new, their impact continues to be largely unappreciated. Appropriately trained nurses can provide an initial filter for referrals to the geneticist and perform an educational role (30). By diagnosing, counselling and treating common CDs, and recognizing and referring more complex disorders as necessary, genetically trained nurses provide a major contribution to genetic services (16, 31). In low resource settings in SA, especially rural areas, nurses in PHC contribute significantly to antenatal, labour and delivery and newborn care. They live and serve locally, understand the local language and culture, and are well respected in the community, making them ideal candidates to be trained as point of care genetic nurses and genetic nurse counsellors (7, 16, 32).

Nurses were identified as a key component of medical genetic services early on in SA. The first genetic nurse was appointed in Durban in 1974 with the mandate to 'find cases, follow-up affected families, create general awareness of genetic services and coordinate existing facilities' (33). By 1977 a network of 16 genetic nurses countrywide had developed and were linked with medical schools, provincial services and their existing clinics and diagnostic laboratories, based around major urban centres (33). Genetic nurses were senior nursing personnel who underwent intensive training to effectively deal with and counsel patients with common congenital disorders. During the late 1970s, the PHC nurse cadre was established enabling nurses with the training and authority to assess and diagnose patients, prescribe treatment and dispense medication (34). Beyond the role of nursing counterparts in high income countries, this was necessity for countries such as SA due to the lack of medical practitioners. *Ad hoc*

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of doctors in South Africa: Is there a role for the private sector in medical education? Hospital Association of South Africa, 2015. http://www.econex.co.za/wp-content/uploads/2015/08/ECONEX_Doctor-shortages-and-training_FINAL.pdf. Accessed 1 February 2016.

[6] University of Cape Town, University of the Free State, University of Stellenbosch, University of the Witwatersrand.

[7] University of Cape Town and the University of the Witwatersrand.

training of genetic nurses spanning a few days to several weeks continued into the 1980s (29).

These genetic services mainly benefited the middle class, white population in urban areas. In 1985 only 18% of the 4 856 patients seen at genetics clinics were black South Africans, despite making up 74% of the country's population (16, 35). Efforts were made in 1990 to expand into more rural areas with no genetics services, but were prevented by budgetary constraints (35).

Collectively, all these factors resulted in genetic nurses becoming the 'back bone' of the genetics service, often working in extremely challenging conditions without medically qualified supervisors, with only five medical geneticists in the country at the time (35).

The Northern Province Experience

The shortfall in medical genetic specialists in SA necessitated outreach programmes to take this expertise where it was lacking. One of the best documented programmes was a clinical genetic outreach in rural Limpopo (then Northern Province) (16, 23). Initiated in 1989, this collaborative project[8] spanned seven years (1989-1996) and reached an estimated fifth of the population of the province (16). By 1992, week-long clinics were held 3-4 times annually by visiting medical geneticists, attended by patients identified by senior nurses trained in genetics. A total of 1 797 patients were seen of which 94.4% were black South Africans (16). The immense need in the Province resulted in the project outreach aims being revised to the development of infrastructure. Genetically trained nursing sisters at the seven collaborating hospitals received further training in 1993 to take up this responsibility. By 1994 they were so clinically adept that common disorders were no longer referred to the visiting medical geneticists at the outreach clinics, which were reserved for cases where 'treatment was available and would significantly improve the prognosis' (16). However, from 1994 commitment and funding to medical genetic services at the provincial level waned and eventually prevented the nurses from continuing in this function (Professor Philip Venter, Personal Communication, 20 May 2016).

Policy changes following the 1994 elections in SA resulted in genetic services being incorporated into primary healthcare countrywide. Genetic nurses were reassigned to PHC clinics where they were expected to provide both genetic and PHC services (31).

[8] Involving the University of the North, the University of Pretoria, National and Provincial Departments of Health and trained nursing staff in seven rural hospitals in the Province.

These changes[9] increased the workload for PHC nurses by an estimated 40% with no additional capacity (36). With an emphasis on HIV/AIDS patients, all nurses were required to primarily focus on providing PHC services, to the detriment of their specialist area (31). The restructuring of the healthcare system to address previous imbalances, combined with competing health needs, resulted in the depletion of posts for both nurse counsellors and medical geneticists (37). Many genetic nurses moved into other positions or emigrated (31). By 2001 only four medical geneticists, less than 20 geneticist counsellors and an unknown number of genetic nurses remained (38).

Although the training of community based nursing staff was identified as a priority for the successful implementation of medical genetic services in the 2001 National Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities (38), formal training of nursing staff in medical genetics has ceased and only sporadic, *ad hoc,* self-funded genetics outreach continues in a few provinces.

Medical genetics in the nursing curricula

With the dismantling of the countrywide network of 16 genetic nurses in the mid-1990s, few genetic nurses and genetic nurse counsellor posts remain countrywide today.[10] With these nurses playing such a key role in genetic services their absence is keenly felt. Research by Phaladi-Digamela to develop a competency based curriculum framework for advanced midwives highlighted the call made by other nursing specialisations that the 'genetic nurse must come back' as they are 'better empowered in addressing genetics problems' (39). This reliance on the genetic nurse stems from inadequate genetics knowledge, skills and competencies included in basic nurse training curricula (38). Appropriate standardised, quality content is lacking, leaving nurses ill-equipped when entering clinical practice (26). Globally these inadequacies are preventing nurses from being prepared for their role in the new genetic era - which calls for *all* nurses to be appropriately skilled in medical genetics (40).

Nursing education reform in SA is continuing as part of the post-apartheid transformation process with the recent incorporation of public nursing colleges into the higher education sector to comply with education legislation (41-43). A continuing Professional Development (CPD) System is also being introduced for nurses, and a Scope

[9] The provision of free healthcare to pregnant women and children under six without medical aid.

[10] Official numbers of genetic nurse and genetic nurse counsellor posts were unavailable. Three genetic nurse counsellor designated posts are known and several other nurses undertake some genetic nurse functions in non-genetic nursing posts.

of Practice is under development for the new nurse categories. However, poor governance by the main institutions involved is delaying implementation and realization of targets outlined in the National Strategic Plan for Nurse Education, Training and Practice 2012/13 – 2016/17 (41, 42). However, this evolving nursing landscape may also be an opportune time to improve the medical genetics component in nursing training.

Key genetics knowledge required by nurses should include: basic scientific principles of genetics; genetic risk assessment; practice and ethics of genetic counselling; accessing genetic information resources; and when to refer, both for appropriate testing and to the medical geneticists or other specialist physicians (13, 32, 44, 45). In SA, it has been established that genetics knowledge is lacking in nursing training (43, 46-49). Genetics education in SA nursing is currently considered as 'slapdash' with a huge variation between institutions according to available facilities and staffing (38, 49). Genetics content is often superficial with little relevance to the identification of CDs, genetic counselling or pre-natal diagnosis (46, 47, 49). A study by Phaladi-Digamela in 2015 indicates that although genetics is included in the curricula of three quarters of the study participants, only 10 hours or less of genetics teaching were reported by 50% of participants, falling far short of the recommended 40 hours (49). The prediction by Godino and Skirton in 2012 that SA will embrace sufficient genetics in the nursing curricula by 2017 is unlikely to be achieved (48). Key challenges include an already full curriculum, nursing faculty/educators lacking genetic knowledge, and genetics education not being considered relevant for nurses (39, 40, 46, 50).

A standardised genetic education framework for nurses is required in SA at both basic and post-basic training levels incorporating both theory and clinical practice components. Such genetic knowledge is required by all nurses, including those in non-specialist healthcare, to translate genetic knowledge and technology to improve healthcare both in PHC and clinical settings (40, 49). Such an increased knowledge base could also serve as a pool from which nurses could then specialise as genetic nurses or genetic nurse counsellors.

The Medical Genetics Education Programme (MGEP)

Since developing such a standardized medical genetics framework is a long-term goal, an interim measure is necessary to equip nurses with genetics knowledge and skills. An existing option that could bridge this shortfall is the Medical Genetics Education Programme (MGEP). MGEP is a post-graduate distance learning, self-administered education programme originally developed in 2003 in response to a recommendation of the Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disability (38). MGEP aimed to equip registered nursing staff, particularly

those involved in maternal, child and women's health, with a comprehensive, primary healthcare medical genetic education (29, 38, 51).

The MGEP programme was developed and piloted by a collaborative team of experts with funding from the March of Dimes (MOD) under the auspices of the Southern African Inherited Disorders Association (SAIDA), a patient advocacy support group recently relaunched as Genetic Alliance South Africa (GA-SA). It was originally intended that MGEP be implemented in two distinct parts over a period of five months, consisting of MGEP 1 and MGEP 2. MGEP 1 focused on theory, over a period of four months with one contact day per month including lectures and practical skills workshops. After the introduction of the Birth Defect Notification Tool (BDNT) in 2006 by NDOH, MGEP 1 also included basic training on completing and submitting BDNT notifications for national surveillance. Successful MGEP 1 participants could undertake MGEP 2, a two-week course focusing on clinical diagnosis and genetic counselling (Prof Arnold Christianson, Personal Communication, June 2016). Due to funding constraints for MGEP 2, in practice only the MGEP 1 component was taught.

Associated with MGEP is a manual *Birth Defects: Counselling and caring for children with birth defects* (52). This distance learning tool promotes independent, home based learning for primary healthcare professionals. The manual was developed with MOD funds collaboratively by a team of medical geneticists, reviewed by the wider medical genetics community and edited and published by Eduhealthcare, as one in a series of self-directed learning course books [www.bettercare.co.za]. With the use of the Birth Defects Manual as a companion resource, MGEP became a successful blend of distance, self-administered home learning and face-to-face teaching.

Between 2004 and 2013 over 1 000 healthcare providers (mainly labour ward nurses) were trained through the MGEP courses held countrywide, with an emphasis on rural areas (11). Coordinated by SAIDA with funding from the NDOH and MOD, MGEP was taught by a team of medical geneticists, genetic counsellors and genetic nurse counsellors. It was intended that successful MGEP participants (nurses) could be further trained to assist with future MGEP teaching. This was formally piloted in Limpopo Province with genetic-trained nursing staff assisting as facilitators of a tele-teaching held MGEP course, resulting in an 86% pass rate of an MGEP 1 course (53).

MGEP Evaluation and Revision

An evaluation of MGEP was undertaken in 2007 for 96 primary healthcare nurses using a pre- and post-course questionnaire to test knowledge and skills (51). Pre-course knowledge averaged at 48% but increased to 75% post-course, and skills pre-course, (eg drawing/interpreting a three-generation family tree), scored an average of 4.5% which

rose to 86% post-course (51). The MGEP contact days of lectures and practical workshops clearly resulted in a significant improvement in skills and knowledge of participating nurses.

Widespread implementation of MGEP ceased in 2014 due to the lack of allocated government funding and of the 1 000 nurses trained in MGEP, less than 100 continue to implement these skills (2). This has directly impacted national surveillance of CDs via the BDNT which was a key area of MGEP trained nurses responsibility. However, some provinces, such as KwaZulu Natal, continue to implement MGEP despite the lack of dedicated funds and the absence of genetic services in the province.

MGEP is currently undergoing a process of revision under the auspices of GA-SA following a request by NDOH in 2014 for an improved medical genetics education course for healthcare professionals. The revised course will comply with Sector Education and Training Authority (SETA) requirements (6 months/six contact days) for future SETA registration to increase the value of the course to participants and to access funding avenues. The Birth Defects Manual is also being simultaneously revised as the Congenital Disorders course book and will be made accessible via the open-source Bettercare website (http://bettercare.co.za) in hard copy, e-version or for free online viewing. Once finalised, both the revised MGEP course and the Congenital Disorders course book will be piloted and evaluated.

Future of MGEP and Birth Defects Manual

The interim use of MGEP and Congenital Disorders course book may be critical in developing the required genetic capacity in nursing and other health care professionals for the beginnings of a universal medical genetics service. To effectively implement the revised MGEP and Congenital Disorders course book, these tools should be integrated into the PHC streams of the National Health Insurance scheme (RSA 2015) as part of the healthcare re-engineering process. While many of the 52 District Clinical Specialist Teams (DCSTs) being established countrywide still lack specialist clinicians, the majority of nursing staff on these teams have already been appointed (54). These PHC, advanced midwifes and advanced paediatric nurses, could receive MGEP training and become genetic ‘champions’ in each district.

To successfully implement such educational programme, much may be learned from other MLIC facing very similar challenges of inadequate capacity and fragmented, heterogeneous services. The CHACO outreach project in Argentina developed a model to introduce genetic healthcare services into PHC in a province lacking genetic services by training 485 health care workers in genetics (55). The CHACO model, which was so

successful that it is being implemented in four additional provinces, uses content very similar to the MGEP course and is adding a distance learning tool (55). This experience highlights a number of factors to consider:

- *Pilot, evaluate and replicate:* Pilot and evaluate MGEP courses prior to scaling up, with continued monitoring and feedback to optimise content.
- *Assess the local situation:* Assess capacity needs in each province/district to identify participants and unique challenges in the area. In SA an audit of genetic services being undertaken by NDOH as part of the 2001 policy revision provides an ideal starting point.
- *Coordinated network approach:* Building and strengthening coordination in each province/district between stakeholders and interventions. In SA this should include the BDNT, the Perinatal Problem Identification Programme (PPIP) and the CHILD Problem Identification Programme (Child PIP) etc.
- *Sustainability:* Training up local trainers to ensure continuous learning opportunities. The education and training mandate of the DCSTs ideally equips them to amplify genetic skills across other PHC streams (Ward-based Primary Health Care Outreach Teams and the school health teams) (Voce *et al*. 2014). Linkages with human genetics academic centres could assist in ensuring quality, standardised training countrywide.
- *Government and provincial commitment:* Both national and provincial government buy-in are required. Scarce specialists (medical geneticists) may be introduced from elsewhere on a regular basis through outreach clinics, permanent posts created and access to genetic technology improved. High turnover of government officials may be overcome by a provincial coordinator role.
- *Hospital management buy-in*: Gaining the commitment from hospital management to ensure continued implementation of the skills acquired.

Future options for the MGEP course include development as an electronic tool through teaching by application on a tablet. Use of such a device would enable an array of other resources to be made available for diagnostic and treatment purposes, including a library of anonymized images to aid diagnosis, similar to the Handbook of Genetic and Congenital Syndromes (56). Limited internet connectivity in rural regions could be overcome by downloading required updated resources periodically.

Conclusion

If used appropriately, widespread MGEP training could swiftly build up a nursing workforce with improved knowledge and skills in medical genetics, as has been modelled by other countries. There remains a need for a formal year-long diploma for specialized genetic nurse counsellors requiring formal accreditation by the South African Nursing Council. In the longer term, SA must follow the global examples of other regions and develop a standardised genetics education framework for integration into the nursing curricula to take advantage of the advances of genetics knowledge and technology in healthcare. With all these tools in place, the role of MGEP could then transition to that of a refresher course and ongoing, in-service training, as an option in the nursing CPD system.

MGEP training could also be implemented for other healthcare professionals to bridge the medical genetics capacity deficit by ensuring doctors are also equipped with the relevant knowledge and skills to work optimally with the MGEP trained nurses. A future goal could be to integrate MGEP content into medical school curricula, with an exit examination a requirement for clinical qualification.

To ensure 'no child is left behind' in the new era of the Sustainable Development Goals (57), the potential offered by these tools must be harnessed to build up medical genetic services countrywide to improve the lives of those affected by CDs in the country.

Compliance with Ethical Guidelines

Funding: Helen Malherbe received a bursary for this study from the College of Health Science, University of KwaZulu Natal.

Conflict of interest: Helen Malherbe is the Honorary Chair of Genetic Alliance South Africa (NPO 001-029). Arnold Christianson, David Woods and Colleen Aldous declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human or animal participants performed by any of the authors.

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Part Five: Global Consensus

Part Five shifts the attention to the global arena and the need for renewed global focus upon CDs within the context of the Sustainable Development Goals (SGDs) (1). This paper was drafted by a core working at the 7th International Conference of Birth Defects and Disabilities in the Developing World held in Dar es Salaam, Tanzania in September 2015. All the issues highlighted in this paper – the need to use standardized definitions and terminology for CDs, improving surveillance and monitoring of CDs, improving pre-pregnancy and pre-natal interventions and care, pre-natal screening and diagnosis, build capacity in medical genetic services, public awareness and education – are also issues that need to be addressed at a national level in SA. Within the framework of the SDGs, there are specific targets that may only be met if the care and prevention of CDs is improved. This includes acknowledging CDs as the first non-communicable disease (NCD) experienced in life if NCDs are to be reduced by two thirds. Similarly, reducing the under-5 mortality rate and reducing preventable newborn deaths requires a renewed focus on CDs

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Chapter 10: Prevention of congenital disorders and care of affected children: A consensus statement

This article was published in JAMA Pediatrics.

Darmstadt GL, Howson CP, Walraven G, Armstrong RW, Blencowe HK, Christianson AL, Kent, A, **Malherbe H**, Murray JC, Padilla CD, Walani SR for the Participant Working Group of the Dar es Salaam Seventh International Conference on Birth Defects and Disabilities in the Developing World. JAMA Pediatrics 2016 Aug 1;170(8):790-3. doi:10.1001/jamapediatrics.2016.0388.

Special Communication

Prevention of Congenital Disorders and Care of Affected Children
A Consensus Statement

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As the Sustainable Development Goals are adopted by United Nations member states, children with congenital disorders remain left behind in policies, programs, research, and funding. Although this finding was recognized by the creation and endorsement of the 63rd World Health Assembly Resolution in 2010 calling on United Nations member states to strengthen prevention of congenital disorders and the improvement of care of those affected, there has been little to no action since then. The Sustainable Development Goals call for the global health and development community to focus first and foremost on the most vulnerable and those left behind in the Millennium Development Goal era. To maximize the opportunity for every woman and couple to have a healthy child and to reduce the mortality and severe disability associated with potentially avoidable congenital disorders and their consequences for the children affected, their families and communities, and national health care systems, we propose priority measures that should be taken urgently to address this issue.

JAMA Pediatr. doi:10.1001/jamapediatrics.2016.0388
Published online June 27, 2016.

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On September 21-24, 2015, the eve of the announcement of the Sustainable Development Goals (SDGs), stakeholders in adolescent, maternal, newborn, and child health and development from 37 countries convened in Dar es Salaam, Tanzania, for the Seventh International Conference on Birth Defects and Disabilities in the Developing World (ICBD) to discuss how to accelerate the prevention of congenital disorders (birth defects, ie, abnormalities of structure or function that are present from birth) and the improvement of care of affected children, especially in high-burden, low-resource settings globally.[1]

This seventh conference, entitled Birth Defects in the Post-MDG [Millennium Development Goals] Era: Joining Hands for Prevention and Care, was organized by March of Dimes in partnership with the Aga Khan Health Services–East Africa, the Aga Khan University–East Africa, US Centers for Disease Control and Prevention, and the Bill & Melinda Gates Foundation. Since the first ICBD in 2001, each conference has been held in a different region of the developing world, with the goal of bringing together experts and stakeholders from the region and from around the world to discuss developments and highlight successes and issues to build capacity in lower-income countries for the prevention of birth defects and preterm birth and improvement of the care of those affected. The conference description, call for abstracts, key deadlines, and related materials were sent out periodically via email lists and the March of Dimes and Centers for Disease Control and Prevention listservs.

The ICBDs were established to focus attention on the need to improve the prevention and care of congenital disorders given that the proportion of deaths in children younger than 5 years due to congenital disorders is rising in many low- and middle-income countries. In addition, rates of disability resulting from congenital disorders are increasing in many countries where newborn survival is improving but quality health care is lagging. Congenital disorders and their associated disabilities result in a substantial emotional, social, and economic toll on affected individuals, their families, and the communities in which they live. The Dar es Salaam ICBD was assembled to agree on actions to reduce this toll, especially in vulnerable, marginalized populations. A draft consensus statement was presented and discussed by the audience on the last day of the conference, with major changes incorporated at that time. The final document was created by the authors and circulated to all conference participants, with 76 providing input and supporting the consensus statement. A working group was also established to explore additional ways to put this statement into action.

We support accelerating the prevention of congenital disorders and improvement of care of affected individuals, recognizing that:

- An estimated 7.9 million children are born each year with a genetic or partially genetic (multifactorial) congenital disorder, and several hundred thousand more are born with congenital disorders due to in utero insults after conception, such as infections, and exposure to teratogens, such as alcohol.[2,3]

- Of the 2.7 million newborns who die annually, more than 1 in 10 die of a congenital disorder, and, overall, there are an estimated 484 000 deaths due to congenital disorders among children younger than 5 years.[4] This number is likely a gross underestimate, however, because many deaths due to congenital disorders, such as heart defects and metabolic disorders, go undetected.
- It is likely that more than 192 000 of the 2.6 million annual stillbirths may result from an underlying congenital disorder.[5] The percentage of stillborn children affected by congenital disorders is likely much higher than for live births, and many efforts to prevent stillbirth will help reduce the occurrence of congenital disorders among stillborn children.
- Most newborns with a serious congenital disorder who survive face a lifetime of severe disability.[2,3]
- An estimated 94% of newborns with 1 or more congenital disorders are born in low- and middle-income countries, placing an additional severe burden on families, communities, and national health care systems.[2,3]
- Up to an estimated 70% of congenital disorders are preventable or their effect can be substantially mitigated and quality of life improved, but these preventive and mitigating actions are occurring almost exclusively in high-income settings.[2,3]
- The fact that children with congenital disorders have been left behind in policies, programs, research, and funding was recognized by the creation and endorsement of the 63rd World Health Assembly Resolution,[6] calling in 2010 for United Nations member states to (1) raise awareness of congenital disorders as a cause of child morbidity and mortality; (2) develop and strengthen birth registration and surveillance for birth defects; (3) strengthen evidence on etiologic factors, diagnosis, and prevention of major birth defects; and (4) develop national plans for implementation of effective interventions to prevent and manage birth defects. This call by the World Health Organization, however, has gone unheeded except in pockets such as Southeast Asia, where a strategic framework[7] is guiding efforts to prevent and control congenital disorders in 12 countries of the region.

The conference participants agreed that, with the advent of the SDGs, greater emphasis must be placed on more holistic approaches, including preventive care and, beyond survival, optimization of childrens' developmental potential. This emphasis aligns with the SDGs' call for equality in social inclusion and in opportunities for education, employment, and the ability for all human beings to fulfill their potential and enjoy prosperous, productive lives. Furthermore, the SDGs call for giving priority in policy and action to the most vulnerable, specifically including those with disabilities, and those currently most left behind.[8] Congenital disorders can be considered the first chronic disease experienced in life and are encompassed in SDG goal 3 that calls for a reduction, by 2030, by one-third in premature mortality from noncommunicable diseases through prevention and treatment and the promotion of mental health and well-being.[7]

Call to Action

To maximize the opportunity for every woman and couple to have a healthy child; to reduce the consequences of potentially avoidable congenital disorders for those affected, their families, the health care system, and the wider society; and to promote the well-being of children who have a congenital disorder, there are many measures that should be taken urgently to address this issue. In this context and in order that no child is left behind, we pledge an initial focus that supports the following:

Improving data quality:

1. Building consensus on and widespread use of a standardized definition of congenital disorders, such as "abnormalities of structure or function, which are present from birth,"[3(p2)] to facilitate data comparison and ensure that the contribution of congenital disorders to the burden of disease is comprehensively represented.
2. Establishing registries and surveillance systems and their integration, where possible, into existing data platforms to monitor the toll and risks of congenital disorders and evaluating the outcome of interventions for prevention and care. Consideration should also be given to the collection of pertinent data available from existing registries and surveillance systems in other countries.

Reducing risk:

1. Promoting family planning, allowing women and couples to choose when they have their first child, space their pregnancies, plan family size, define the ages at which they wish to complete their family, and reduce the proportion of unintended pregnancies.
2. Ensuring a healthy, balanced diet for girls and during a woman's reproductive years through an adequate intake of macronutrients (protein, carbohydrates, and fats) and a broad range of micronutrients. Special attention should be given to adding 400 μg of synthetic folic acid daily to the diet through fortification and supplementation while also promoting a diet rich in food folates, correcting iodine deficiency through fortification, and ensuring iron sufficiency through fortification, supplementation, and therapy for those with deficiencies.
3. Removing teratogenic substances from the diet, the most important of which is alcohol, and minimizing environmental contaminants in foods.
4. Controlling infections in women of reproductive age, including rubella and syphilis, and optimizing maternal health through detection and management of chronic illnesses associated with an increased risk of congenital disorders, such as type 2 diabetes mellitus and epilepsy, which require teratogenic medications.

Improving care:

1. Training physicians, nurses, allied health care professionals, and workers in the fundamentals of the recognition, causes, and care of children with congenital disorders and ensuring physical examinations of all newborns by trained health care professionals before discharge from the hospital or clinic.
2. Aligning medical and social services to provide timely treatments for congenital disorders, including surgery, medications, dietary modifications, and rehabilitation services when needed.
3. Providing emotional and practical support for parents to enable them to understand and manage their risk of congenital disorders and to help families in supporting the growth and development of children with congenital disorders.

Empowering the public and civil society:

1. Educating the public about congenital disorders and the steps mothers and fathers can take with their health care professionals to maximize the chances of a healthy pregnancy.

2. Strengthening civil society—including patient and parent support groups, faith-based groups, and nongovernmental organizations—to advocate for improved prevention of congenital disorders and access to high-quality, family-centered patient care, including facilitating community and professional awareness and education and advocating for increased funding for research on the causes of congenital disorders.

The following additional actions should be taken by countries as priorities and circumstances allow:

1. Training physicians, nurses, and allied health care professionals in the essentials of medical genetics. This training should include diagnosis of common congenital disorders before and at birth; means of treatment where possible in the primary health care setting; knowing when to refer a patient for more specialized treatment; basic genetic counseling, including best practices in communicating unfavorable health information to parents; and support for families who have a child or are at risk of having a child with a congenital disorder. Genetic counseling aims to empower those who are counseled to make autonomous decisions regarding their health in ways that are consonant with their religious and ethical beliefs and circumstances and to support them in their decisions.
2. Establishing periconception medical services to assist women and their partners in attaining optimal physical and mental health and well-being and to facilitate a healthy pregnancy and delivery of a healthy infant. These services include rubella immunization; screening for the risk of genetic, partially genetic, and teratogenic congenital disorders; and mental health counseling, including identification and support for depression.
3. Implementing preconception or prenatal medical screening to identify women and couples at risk of having a baby with hemoglobin disorders; Down syndrome; blood type incompatibility; congenital sexually transmitted infections such as syphilis, human immunodeficiency virus, and herpes simplex virus; and structural malformations, particularly neural tube defects.
4. Establishing newborn screening to identify congenital hypothyroidism, phenylketonuria, galactosemia, sickle cell disease, glucose-6-phosphate dehydrogenase deficiency, and other metabolic disorders.
5. Supporting research into the diagnosis, prevention, etiologic factors, and treatment of congenital disorders to enable improved outcomes for children into the future.

The conference participants call for concerted action by international government policymakers and donor organizations to explore how these recommended actions can be funded through more cost-effective and rational integration of policy, funding, and interventions across the reproductive, maternal, newborn, child, and adolescent continuum. Systems are required that encourage more effective partnership among the many existing organizations and agencies whose missions address common risk factors and outcomes and who would benefit financially and programmatically from better integration of policy, research, and action at international and national levels.

Conclusions

The Seventh ICBD in Dar es Salaam, Tanzania, was a pivotal opportunity to build consensus and commitment for accelerated prevention of congenital disorders and improvement of care of affected children in low- and middle-income countries. In conjunction with the newly launched SDGs and building on the 63rd World Health Assembly resolution calling on United Nations member states to strengthen prevention and care for congenital disorders, immediate action on the plan outlined above will save newborn and child lives, reduce disability rates and improve quality of life in survivors, and substantially lessen the current emotional and economic toll of these conditions on affected individuals, their families, and the communities in which they live.

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Accepted for Publication: February 9, 2016.

Published Online: June 27, 2016. doi:10.1001/jamapediatrics.2016.0388.

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Conflict of Interest Disclosures: None reported.

Funding/Support: The Seventh International Conference on Birth Defects and Disabilities in the Developing World was supported in part by a grant from the March of Dimes Foundation, grant number 5U38OT000199 from the US Centers for Disease Control and Prevention, and the Bill & Melinda Gates Foundation (Investment ID OPP1129127).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Additional Contributions: Megan Bruno and Randi Roberts, March of Dimes Foundation, provided administrative support in the preparation of the manuscript. They were not compensated for their contribution.

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Chapter 11: Discussion

Rational and Aim of Study

Congenital disorders (CDs) are a common, costly and critical health issue. In South Africa (SA) and many other middle and low income countries (MLIC), they remain unprioritised, their contribution to the health burden underestimated, and services for their care and prevention are neglected. This results in often preventable human suffering, impacts the human rights and dignity of those affected or at risk of being affected, and comes with significant socioeconomic effects. Medical genetic services for the care and prevention of CDs in SA require measured consideration and strategic planning to meet the growing health need in the current epidemiological and socioeconomic context.

On the basis of this rationale, this PhD study aimed to investigate the renewed need for the care and prevention of CDs in SA. This was undertaken through a series of in-depth studies on specific sub-topics to evaluate the overall requirement for medical genetic services in the country. This followed a logical step-wise process including: why these services are needed (epidemiology); how these services are provided for legislatively (legal framework); how CDs relate to other health priorities (child mortality); quantifying the health burden of CDs (modelled data); responding to the challenge (capacity building); and, the global context for the health issue of CDs (global consensus).

Synthesis of Findings

Collectively, these individual studies have built up an overall picture of the situation of CDs in SA and the current state of medical genetic services. As outlined in the first paper in Chapter 3, the impact of the HIV/AIDS and TB epidemics on epidemiological transition in SA was substantial and to the detriment of the developing medical genetic services. The data presented indicated that the country is back in positive transition once again, a finding which is consistent with other studies (1). Chapter 3 also highlighted the current infant mortality rate (IMR) in SA, of 27 per 1 000 live births (2) as being well under the threshold of 40-50 per 1 000 live births, when medical genetic services are usually developed (3-7). Despite the extensive literature supporting this concept of a designated stage for developing these services, this is yet to be recognised by SA and is an important finding of this study.

The protracted epidemiological transition SA is experiencing describes the persisting burden of communicable diseases in parallel to emerging non-communicable diseases

(NCDs) (1, 8-10). This has contributed to the delay in developing medical genetic services in SA, which is confirmed in the literature most recently by Sitkin *et al* (11). Although the burden of CDs remains largely obscured by communicable disease, the growing proportion of deaths from CDs as the country develops and IMR decreases is an irrefutable trend already in progress in SA (12). While this may be a more extended process in SA and other MLIC due to the persisting burden of infectious disease in comparison to the classic transition experienced by industrialised countries, the same end results.

Within this context, Chapter 4 aimed to identify the legislative framework relevant to medical genetic services for the care and prevention of CDs. There seems to be little awareness by policy makers of the key international document, World Health Assembly Resolution 63.17 (WHA 63.17) of 2010 (13), to which SA is a signatory as a United Nations member state. The WHA 63.17 call to prioritise the care and prevention of CDs has gone largely unheeded in SA, as evidenced by the lack of inclusion in national strategy (14, 15), the lack of implementation of existing policy (16), and delays in revising policy relevant to CDs.

A surprising finding of the desktop review of legislation in Chapter 4 was the specific provision for genetic services in the National Health Act (NHA) 61 of 2003 (17). Prior to this study, the widely-held view of the literature indicated the most relevant content of the NHA as the provision of free health services for pregnant and breastfeeding women and children under the age of 6 (that are not members of medical aid schemes) (17). This NHA directive to provide genetic services is crucial, and holds together the provisions in all other legislation.

Although a comprehensive legislative framework exists in SA for the provision of medical genetic services there is a shortfall in the implementation of these services. The underlying reason for this shortfall is the lack of recognition of the burden of disease represented by CDs. This finding is an issue shared by many MLIC, a fact borne out in the literature, with the lack of empiric data in SA on CDs from surveillance systems a major contributing factor (3, 6, 13, 18-23).

The lack of awareness of the status of medical genetic services by policy makers prompted a critique of the 2015 Guidelines for Maternity Care (24) in Chapter 5. While the inclusion of referral services in these guidelines for advanced maternal age and other high-risk categories is relevant, there was little cognisance of the insufficient capacity available to provide these services in practice. The disconnect between the developers of these guidelines and the medical genetics community was in stark contrast to the consultative process undertaken to compile the 2001 Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth defects and Disabilities (16).

Inadequate capacity of the medical genetic services sector was an issue highlighted in many of the Chapters of this study. A comparison of capacity available in the sector today compared with 2001 was included in Chapters 4 and 6. The finding that capacity today is at a lower base than in 2001, despite the increased population, is consistent with the work by Kromberg *et al* (25) who indicated that current limited capacity is only enabling 10% of the country's genetic needs to be met. Without an adequate workforce, the implementation of basic medical genetic services, including the diagnosis, care and prevention of CDs will continue to decline.

The contribution of CDs to child mortality in SA is an issue that warranted further investigation and was the focus of Chapter 6. This was prompted by the stagnation in neonatal, infant and child mortality rates in the country since 2011, despite continued interventions to treat communicable diseases (26, 27). This suggests other, unaddressed health issues contributing to child mortality, and CDs were presented as the first of these. This is consistent with the literature, which clearly demonstrates an increasing proportion of deaths from CDs as the IMR decreases (12, 28-30). A key finding of Chapter 6 was the emergence of CDs as a leading cause of death in SA, with CDs having overtaken infection and ranking 3rd as a cause of death in early neonatal deaths in the Western Cape (31). This is of particular significance as the Western Cape province leads the country in health service provision and serves as a proxy for where the rest of the country will follow in the future. Surprisingly, although this change in rankings was reported in the public sphere, its significance does not appear to be fully appreciated (31). This is indicative of the lack of cognisance of the contribution of CDs to child mortality and the potential significant reductions that may be achieved by improving medical genetic services. Instead, efforts to reduce child mortality are focused on other interventions, termed 'low hanging fruits', such as those outlined by Chola *et al* (32). The most important finding of Chapter 6, is that for child mortality to be further *significantly* reduced in SA, medical genetic services for the care and prevention of CDs must be comprehensibly implemented. This is consistent with the literature (3-7).

A theme emerging throughout the course of this study is the issue of terminology and definitions of CDs. A lack of clarity has led to the use of disparate and non-synonymous terms by stakeholders both globally and locally. This issue is highlighted in several Chapters of this study, but is of most relevance in Chapter 7. The letter to the journal editor in response to mortality data published in a specific region of the Western Cape demonstrated the inadequacies of the current 10th edition of the International Classification of Diseases (ICD-10) (33) with relevance to CDs. The prolific use of the term *congenital anomalies* (and equivalent terms) to represent the totality of CDs, despite excluding an estimated 40% of CDs within the ICD-10 system, is a key finding in sync with

other published work (13, 34, 35). If only a portion of CDs are being reported, this contributes to underreporting and prevents an accurate estimate of the true disease burden – since not all CDs are represented. This has implications for ranking in overall mortality assessments and cause of death studies both nationally and globally.

A further issue related to terminology is the exclusion of CDs from specific NCD policies and interventions (14, 15, 36). The reluctance to contextualize CDs as an NCD in SA is at odds with the global classification of CDs as an NCD as reported in the literature (37) (38). Instead, the promotion of a newly coined term *long-term health conditions* (39, 40) in children combines CDs with acquired conditions, and states that the NCDs classification is not applicable for children. This further diminishes the issue of CDs and has implications for the development of and access to cogent medical genetic services, including multifactorial (complex) CDs which tend to manifest later in life.

The lack of empiric data for CDs in SA, as highlighted by Lebese *et al* (18), has been an issue that has dominated this study. Without these data there is little evidence to persuade policy makers of the burden of disease represented by CDs, preventing the required commitment for services to be developed. Chapter 8 aimed to rectify this by quantifying the scale of the problem represented by CDs using modelled estimates. The resulting estimates clearly demonstrate the impact of care and preventative interventions on reducing mortality and mitigating morbidity. This dispels the myth that *nothing can be done* for those affected by CDs. This key finding demonstrated that even with a national average of only 30% access to optimal services, a substantial number of lives can be saved and degree of disability reduced. This was consistent with studies by Czeizel *et al* (41) and Christianson and Modell (19), which indicate that up to 70% of CDs can be prevented, cured or disability ameliorated. With the increase in survivors comes an increase in the cost of care, due to a greater number living with disability. This finding was consistent with the literature, most notably Christianson *et al* (29), which highlights the importance of balancing care and prevention.

The issue of capacity is revisited in Chapter 9 with the suggestion of a potential solution for rapidly increasing capacity in the sector. The shortcomings of genetic education of health care professionals (HCP) in SA is similar the world over, as confirmed by the literature (42). The key finding of this Chapter is the availability of two genetic education tools that may be used to swiftly train large numbers of nurses as a short-term measure to up-skill the medical genetics sector. The proven track record of the Medical Genetics Education Programme (MGEP) and the Congenital Disorders Handbook, and the experience of similar tools in other countries is borne out in the literature (43, 44). It is imperative that this capacity building is undertaken within the context of the PHC streams of the National Health Insurance (NHI) initiative (45) to ensure full integration, sustainability and universal availability of medical genetic services in the future.

Chapter 10 provides the global context for CDs and the need for improved medical genetic services against the backdrop of the Sustainable Development Goals (SDGs) (46). For SA, the SDG 3 target to reduce the current under-5 mortality rate (U5MR) from 39 to 25 deaths per 1 000 live births (26, 46) will require the comprehensive development of medical genetic services to tackle the burden of CDs. SA has already reached the SDG 3 target for neonatal deaths of 12 per 1 000 live births (26, 46). However, with over 40% of under-5 deaths occurring during the first month of life in SA (47), this highlights the need for further study and the potential contribution of undiagnosed CDs to these deaths. If the SDG 3 target to reduce NCDs by two-thirds by 2030 (46) is to be reached in SA, it may require an adjustment of the classification of CDs as an NCD. Remarkably, the challenges highlighted globally in the consensus document were found to be the same as those faced nationally by SA. This was consistent with the literature, which has been making the same call to action to policy makers for decades (3, 6, 19-23, 29).

In the words of WHO (21) 'It appears that one of the main problems in delivering genetics services is the difficulty of informing the profession and the community of the real significance of genetic problems.' The first step in this process is the realisation of the true burden of CDs. This is necessary to generate the required political commitment in SA for the further development of medical genetic services. Without this commitment and renewed, comprehensive services streamlined across the continuum of care (48), SA will remain ill-prepared for the growing health need of CDs.

Contribution to Knowledge

This study has made the following original contributions to the literature and the advancement of knowledge:

- A macro-scale situational analysis of CDs in SA, that is to date, unprecedented. The specific data, concepts and perspectives presented are drawn from the international and national scientific literature, and world-renowned experts to provide the current South African context regarding medical genetic services.
- The identification of the national legislative and regulatory framework relevant to CDs is a blueprint for future monitoring of policy implementation and a point of reference for new policy development. It may also serve as a key advocacy tool for civil society and underserved patients.

- This study has highlighted the contribution of CDs to child mortality, and demonstrated the lack of cognisance around the growing proportion of CD related deaths as the country transitions epidemiologically.
- The lack of empiric data on CDs in SA is a major factor contributing to the inaccurate assessment of the CD disease burden in SA. By quantifying the burden of CDs in SA through modelled data, the findings of this study provide a baseline for further studies to measure the impact of care and prevention interventions, and serve as a target for future surveillance systems.
- By quantifying the diminished capacity in the medical genetic sector, this study has documented the lack of investment in the sector and the urgent need to rectify this situation through capacity building. By proposing a means to achieve this, the study has also offered a potential solution for increasing capacity in the sector.

Study Limitations

It is acknowledged that as a desktop study this PhD is limited to theoretical knowledge.

The methodologies used to develop epidemiological estimates in this study are subject to the limitations of the Modell Global Database (MGDb). These methods are detailed in a forthcoming series of articles in a special edition of the Journal of Community Genetics (49).

Study Implications

It is hoped that relevant government organisations will respond to the arguments presented in this study, including the proposal to improve the quality of genetic education in nurse training as an integral part of the NHI.

Conclusions

This study investigated the need for renewed services for the care and prevention of CDs in SA. The overall finding of this study is that there is an urgent need to renew medical genetic services in SA since:

- There is a lack of recognition of the contribution of CDs to the burden of disease in SA and to child mortality.
- SA is beyond the designated stage at which genetic services are developed (IMR of 40-15 deaths per 1 000 live births).
- Currently stagnated child mortality in SA will only *significantly* be further reduced by addressing CDs through developing improved medical genetic services.
- Current surveillance is substantially underreporting CDs and urgently requires revision.

- Modelled estimates of CDs provide a baseline estimate in the absence of accurate empiric data, and demonstrate that intervention can save lives and mitigate disability, although the cost of care may increase.
- Current capacity in the medical genetics sector is inadequate. Use of the MGEP and the Congenital Disorders Handbook within the context of the re-engineering of PHC are potential tools that could be used to swiftly increase capacity by training nurses.
- Confusion around terminology and definitions related to CDs needs to be clarified and the usage of appropriate terms agreed to minimize underreporting to enable data comparison. This should include the classification of CDs as an NCD.

Recommendations:

Policy Recommendations

The key policy recommendation emerging from this study is the need for increased political commitment to medical genetic services for the care and prevention of CDs in SA. This needs to be accompanied by appropriate allocation of resources with actionable tasks related to improving surveillance and monitoring of CDs and capacity building, making measure for post allocation and funding.

Future research

Areas for future research prompted by this study include further modelling studies at the provincial level and for specific CDs in SA. A further phase of this work could include the development of cost estimates for specific interventions to illustrate the socioeconomic impact and cost effectiveness of medical genetic services.

Developing consensus in SA on the use of standardised terminology and definitions for CDs is necessary to ensure accurate reporting of CDs to reduce the underestimation of CDs to the disease burden. This needs to be evaluated within the context of the 11th revision of the ICD system.

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Appendices

Appendix 1: The Study Protocol

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An investigation into the renewed need for the care and prevention of congenital disorders in South Africa.

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3 April 2017

Executive Summary

The current state of genetic services in South Africa (SA) related to the care and prevention of congenital disorders (CDs) are in decline due to competing health priorities. Currently available services are inadequate to service the population and this must be rectified to meet the increasing health need as CDs emerge as a leading cause of death in children in SA,. Many of those born with a CD remain undiagnosed or are misdiagnosed and die as a result, with the cause of death incorrectly assigned, while others survive with lifelong disabilities due to inadequate care.

This project will investigate CDs and the required services in SA, providing a comprehensive, evidence based evaluation of this neglected health issue that contributes significantly to the disease burden. Undertaken as seven distinct tasks, the first of these will describe epidemiological transition over the past 25 years in SA and contextualise CDs demonstrating their contribution to child mortality and morbidity. The lack of comprehensive data on CDs in SA will be supplemented by the second task of modelling data and mapping the burden of birth prevalence and outcomes of CDs in the country. The third will investigate the legal, constitutional and regulatory imperatives, highlighting the rights of those affected by CDs, and evaluate the existing legal framework in place and its current implementation inluding any shortfalls. Tasks four and five focus on the need to build medical genetics capacity in clinical staff to improve diagnose, care and prevention of CDs. Educational frameworks based around core genetic competencies will be developed for both doctors and nurses to serve as resource for curricula and skills development. To be reported, CDs must first be recognised and diagnosed accurately and this can only be achieved if clinicians primary health care providers are trained adequately. Medical genetics education in SA with the UK will be compared in as a sixth task, aiming to identify gaps in current training in SA and to learn from the UK, an industrialised nation in later stages of epidemiological transition where CDs emerged and remained as a leading cause of mortality in children.The final task will draw together the findings of the seven tasks and outline potential steps forward that are required to renew genetic services in SA related to CDs.

The outputs of this project will include seven peer-reviewed publications reflecting the seven tasks outlined above and a number of presentations at relevant national, regional and international conferences. A concise report outlining the findings and recommendations for the renewal of genetic services will be submitted to the National Department of Health. The educational frameworks developed will also be distributed to medical training institutions as relevant.

By providing an evidence-based evaluation, this study can contribute to CDs being once again prioritized as a health care issue in accordance with World Health Assembly (WHA) Resolution WHA63.17, and influence policy and decision makers to leverage political commitment, support, and the required resources to develop and implement the required genetic services. The ultimate impact should be the provision of relevant, effective services for the care and prevention of CDs, to achieve the human dignity, and constitutionally and legally enshrined human rights of people affected and their families.

Table of Contents

1) Defining the Research Problem

As South Africa (SA) undergoes epidemiological transition and non-communicable diseases are better controlled and cause less deaths overall, the proportion of deaths caused by congenital disorders (CDs) is increasing and they are emerging as a leading cause of mortality and morbidity in children [1].

As services for the competing health priorities of HIV/AIDS and concomitant TB developed over the past 10-15 years, this diverted funding and attention from CDs. Tertiary medical genetic services required for the care and prevention of CDs declined [2] are now severely compromised in SA. Many of those born with serious CDs in SA remain undiagnosed or are misdiagnosed and die with the cause of death incorrectly assigned [3] or survive with severe disabilities due to inadequate care. Currently, less than 4 % of CDs are reported via the Birth Defect Collection Tool administered by the Department of Health (Ms V Mtyongwe, personal communication). This lack of accurate data has contributed to an underestimation of the contribution of CDs to the burden of disease and a lack of political will in prioritising their care and prevention, further exacerbating the problem [4].

Up to 70 % of serious CDs can be prevented, cured or ameliorated by appropriate care, [5] but CDs must first be recognised, referred and diagnosed [1]. Existing clinical expertise to enable this in the health care system is inadequate and training is required in medical genetics to equip healthcare providers throughout the continuum of care. This capacity is a necessay componant of developing comprehensive genetic services to counter the burden of disease resulting from CDs.

2) Literature Review and Motivation

A congenital disorder (CD) is "*any abnormality affecting body structure or function, including metabolism, which are present from birth, whether recognised at birth or later*" [1,6]. The causes of CDs are diverse. Some are caused pre-conception by genetics, and others are caused post-conception by maternal exposure to environmental agents (radiation, methyl mercury), teratogens including alcohol and drugs, maternal illness including diabetes and epilepsy and maternal infections such as cytomegalovirus, herpes, HIV/AIDS, rubella, toxoplasmosis, varicella virus etc, which affect the developing fetus [1]. Others are thought to be a combination of genetics and the environment although the exact cause is unknown.

The March of Dimes Global Report on Birth Defects [1] estimates that globally 9 million infants (7 % of live births) are born annually with a serious CD leading to death or lifelong disabilities. Births affected by these disorders are not equally distributed around the world, with over 90 % born in middle or low Income countries. This imbalance is attributed to poverty and differences in maternal health, including a greater frequency of consanguineous marriages, a high percentage of older mothers and the survival advantage against malaria for carriers of sickle cell, thalassemia, and glucose-6-phosphate dehydro-genase (G6PD) deficiency genes [1]. As a result of inadequate care in

these MLIC, 95 % of these die including 3.3 million children under the age of five - and a further 3.2 million survive and are disabled for life [1,7].

Historically, the significance of CDs has long been underestimated and neglected, especially in MLIC where they continue to be a '*serious, unappreciated health problem causing a significant health burden'* [1]. Many MLIC, including SA, have not achieved significant progress in controlling CDs and are in the midst of epidemiological transition, a process that industrialised countries completed decades ago [8]. During this transition, infectious diseases are contained, and malnutrition and poor healthcare (including maternal) services are reduced, resulting in lower mortality and less "unnecessary" deaths. Deaths from CDs usually remain invisible - "buried" among deaths caused by communicable diseases and only emerge as these diseases are adequately controlled. As industrialised countries moved through the early stages of epidemiological transition, the birth prevalence and deaths from CDs due to fetal environmental factors, essentially teratogens, decreased slightly, due to improved care and prevention strategies, such as education and screening [1]. However as 85 -90% of CDs have a genetic or partially genetic aetiology, their birth prevalence and resulting mortality remained high.[1] In these industrialised countries, deaths from these disorders became proportionately greater in overall neonatal, infant and child mortality as deaths from communicable diseases reduced as they were contained and eventually eradicated. CDs emerged as a leading cause of child mortality and remain a leading cause of child death in these nations today [9].

In SA, modelled data of genetic causes of CDs [1] and an estimate of teratogenic causes (Prof AL Christianson, personal communication) indicates a minimum of 6.8 % of births, representing one in every 15 live births, is affected by a CD. Of these, 80.5 % are genetic/partially genetic in cause while 19.5 % are caused by teratogens. The latter is more than the 10-15 % expected owing to the high prevalence of Fetal Alcohol Syndrome (FAS) [1]. With 26.2 % of CDs diagnosable in the first day of life, over 18 000 cases annually should be identified and reported in SA [10]. However, in 2012 only 2 174 CDs were documented via the Birth Defects Collection Tool (BDCT) administered by the National Department of Health (NDoH) (Ms V Mtyongwe, personal communication).

CDs contribute significantly to the under-five mortality rate (U5MR) which indicates the probability of dying between birth and five years of age per 1000 live births of the population. Globally, the U5MR has almost halved since 1990, decreasing from 90 deaths per 1000 live births to 48 in 2012 which translates to 6.6 million children under five dying in 2012 compared to 12.6 million in 1990 [11]. However, as the overall U5MR declines, the proportion of deaths occurring during the neonatal period (the first 28 days of life) is increasing and is now over 40 %, of which 9 % is attributed to CDs [11] . However, with many CDs remaining undiagnosed and the cause of death often misdiagnosed in MLIC due to inadequate clinical expertise available, it is likely that the 9 % attributed to CDs as cause of death is an understimate.

Global efforts are underway to reduce the number of child deaths. Efforts include the Millennium Development Goals (MDG) set in 2000, especially MDG4 which commits to reducing the number of the U5MR by two thirds between 1990 and 2015. The SA target U5MR of 20/1000 live births will not be met, although much has been done to counter the initial rise in child mortality in the 2000's caused by HIV/AIDS [12]. Since their implementation in the mid-2000's, scaled-up prevention of

mother-to-child transmission and expanded roll-out of antiretroviral therapy saw rapid and significant reductions in both the U5MR and infant mortality rates, [12] which dropped from 74/1000 live births and 52/1000 live births in 2000 to 44/1000 and 33/1000 respectively by 2012/13 [13]. However, since 2011 these child mortality rates have stagnated [14] indicating other health issues that need to be addressed to further reduce child mortality, such as the care and prevention of CDs. The current IMR of 33/1000 live births [13] is below the range of between 40-50 deaths per 1000 live births when countries recognise the coming health need of CDs and services for their care and prevention and well below 40 per 1000 live births when these services should have been implemented. [15]

For CDs, one of the most significant global political shifts was in 2010 when the World Health Organization's (WHO) highest decision making body – the World Health Assembly (WHA) - prioritized services for the care and prevention of CDs, particularly in MLIC, by passing Resolution WHA63.17.[16] This Resolution recognised the importance of CDs as a cause of stillbirths and neonatal deaths, their contribution to under-five mortality and contribution to failure to attain Millennium Development Goal 4 (MDG4). WHA63.17 urged member states (including SA) to recognise and address CDs as a public health issue. The Resolution also highlighted the lack of accurate epidemiological data available for many MLIC which prevents policy/decision makers from correctly assessing the burden of CDs in these MLICs.[4, 16]

Genetic services were initiated in the 1950s and 60s financed by the State under the Health Act (Act 63 of 1977) including laboratory services, community screening for specific conditions, community education and training programmes and the establishment of several academic centres [2]. However, it was only in the early 1990's due to falling childhood mortality, that CDs began to emerge as a public health issue. In 2001, Policy Guidelines for the Management and Prevention of Genetic Disorders, Birth Defects and Disabilities were published by the DoH, aiming to "*deliver a comprehensive genetic service equitably to all South Africans*" [17] . Developed through wide consultation and input by national, provincial DoH representatives and academics, the Guidelines outlined goals, objectives, strategies and delivery of genetics services for the prevention and care of genetics services relevant for SA [17]. Personnel requirements to implement these services were also specified in the Guidelines, based on UK criteria, and were later revised using more relevant criteria for SA in the Strategic Framework for the Modernisation of Tertiary Hospital Services. [18] Four years later, In 2004 the National Guidelines for the Care and Prevention of the Most Common Genetic Disorders, Birth Defects and Disabilities were published, targeting Primary Health Care Providers (PHCP), and described common CDs and strategies for their care and prevention [19].

The HIV/AIDS epidemic then buried CDs as a health care issue, and a consequence, funds and attention were diverted from the care and prevention of CDs to this competing health priority. As services for HIV/AIDS developed over the past decade, tertiary medical genetic services have been simultaneously neglected. In 2013, SA was reported as the only country of eight emerging economies evaluated where positive development in improving medical genetic service structures had ceased and indeed retrogressed [4].

Although reducing maternal and child mortality is a key strategic outcome for the SA health sector, as specified in the Negotiated Service Level Agreement and tackled in relevant strategies, policy and by relevant established bodies, including the Strategic Plan for Maternal, Newborn, Child and

Women's Health (WNCWH) and Nutrition in South Africa 2012-2016 [20], the Department of Health Strategic Plan 2-14/15 to 2018/19 [21] The Committee on Mortality and Morbidity in Children (CoMMiC), South Africa's National Plan for The Campaign on Accelerated Reduction of Maternal and Child Mortality in Africa (CARMMA) [22], and the Child Perinatal Problem Identification Programme (Child PPIP). However, although several include a CD statistic, none of these initiatives include CDs as a health issue or relevant strategies for their care and prevention. Nor do they respond to the Resolution WHA63.17 [16], legally required as a WHO member country.

The purpose of this study is to investigate the renewed need for services for the care and prevention of CDs in SA. Epidemiological transition in SA will be examined over the past 25 years. Data will also be modelled in more detail to indicate the scale of CDs as a health care issue in SA. Genetic education needs of relevant health care professionals will also be evaluated and a competence based education framework developed. Collectively, the papers published from this research will provide a comprehensive and evidence based overview of the issue of CDs and the current situation of genetic services in SA, including needs in medical genetics education.

3) Aim and Objectives

Aim 1: The renewed need for care & prevention of CDs in SA: Epidemiological transition

Objectives:

- To provide an overview of CDs in SA and their significant contribution to mortality and morbidity.
- To explain the process of epidemiological transition in SA over the last 25 years using relevant national demographic data.
- Demonstrated the impact of the counter epidemiological transition on medical genetic services, including examples of current inadequate services available.
- Highlight what is required to develop and implement relevant services in the community.

Aim 2: The renewed need for care & prevention of CDs in SA: Constitutional, legal and regulatory imperatives

Objectives:

- A desktop study will be undertaken to identify all relevant constitutional, legal and regulatory documents relating to the provision of medical genetic services in SA.
- The specific extracts of these documents will be evaluated in the context of the current services available to identify the legal and ethical shortcomings of the current services being provided.

Aim 3: The renewed need for care & prevention of CDs in SA: Mapping the burden of CDs in SA.

Objectives:

- South African demographic data will be obtained from Stats SA for a discrete time interval (one year period). Where possible, provincial and district data will be used to enable regional variations to be identified.
- The Modell Global Database of CDs will be used and adapted to model this data to map the birth prevalence and outcomes of CDs for SA. This will include a variety of different scenarios, i.e. with and without adequate intervention to demonstrate the best and worst case scenarios possible for SA.
- The findings of this exercise will be made public to highlight the contribution of CDs to the country's disease burden.

Aim 4: The renewed need for care & prevention of CDs in SA: Educational framework for undergraduate and post-graduate nursing genetic education.

Objectives:

- Existing core competencies for nurses developed elsewhere in the world (e.g. UK) will be evaluated for use and cross-referenced with other relevant content identified in recent SA fora. The resulting list will be used as the starting document for evaluation.
- A rigorous consultation process will evaluate and refine the starting document and will involve wide consultation with relevant role players, including the Council of Nurses and other relevant educational bodies, through a multi-step process.
- The resulting framework of core competencies and learning areas on medical genetics (CDs) will be published and used as a resource for developing curricula for undergraduate and post-graduate nurse training.

Aim 5: The renewed need for care & prevention of CDs in SA: Educational framework for undergraduate medical genetic education.

Objectives:

- Existing core competencies for doctors (non-genetic specialists) developed elsewhere in the world (e.g. Uk) will be evaluated for use and cross-referenced with other relevant content identified in recent SA fora. The resulting list will be used as the starting document for evaluation.
- A rigorous consultation process will evaluate and refine the starting document and will involve wide consultation with relevant role players through a multi-step process.
- The resulting framework of core competencies and learning areas on medical genetics (CDs) will be published and used as a resource for developing curricula for medical schools.

Aim 6: A review of medical genetic education in SA- a comparison with the UK.

Objectives:

- The genetics/genomics content of medical school curricula will be evaluated and assessed for relevance to providing adequate genetic services related to CDs at key medical schools in the UK and in SA.
- Commonalities and differences in content and format will be identified and discussed, and the relevance of the resulting education to the provision of genetic services related to CDs.

Aim 7: The renewed need for care & prevention of CDs in SA: A way forward

Objectives:

- All the work undertaken as part of this project will be taken into account and an article written to give an overview of the findings and the potential steps forward that are required to renew genetic services in SA related to CDs.

4) Methods

4.1 Study Design for Research Aim 1: Epidemiological transition

This is an observational study. The systematic review of literature on epidemiological transition in MLIC and industrialised countries, as well as research of child mortality, life expectancy at birth (longevity) and HIV/AIDS prevalence in pregnant women will be conducted by accessing research from journal articles published in peer-reviewed journals and relevant publicly available international data sets will be downloaded for evaluation.

4.1.1 Setting

Data relevant to epidemiological transition in SA will be reviewed, although statistics maybe sourced from other countries as relevant to enable comparisons.

4.1.2 Research Object Selection

The timeframe of the past 25 years has been selected for this study, specifically from 1988 – 2013. The start of this timeframe falls immediately prior to the start of the HIV/AIDS epidemic, when childhood mortality was decreasing and longevity increasing.

4.1.3 Measurements

The Infant mortality rate, under-five mortality rate, longevity (average for males and females) will be used for the past 25 years in SA. Figures of HIV infected pre-natal women will be used as an as an indicator of HIV/AIDS prevalence over the same period.

Online data sources will include:

- UN Inter-agency Group for Child Mortality Estimation (www.childmortality.org);
- World Bank longevity data (http://data.worldbank.org/indicator/SP.DYN.LE00.IN)
- HIV data from the 2012 National Antenatal Sentinel HIV and Herpes Simplex type-2 prevalence Survey, National Department of Health, SA. (www.hst.org.za/publications/2012-national-antenatal-sentinel-hiv-herpes-simplex-type-2-prevalence-survey).

4.1.4 Data Analysis

The data sets will be represented graphically to demonstrate the process of epidemiological transition in SA over the past 25 years. Descriptive statistics and analysis will be used to describe the changes in mortality and longevity over this period and the interplay with the HIV/AIDS epidemic and treatment.

4.2 Study Design for Research Aim 2: Constitutional, legal and regulatory imperatives

This is an observational study and aims to describe the constitutional, legal and regulatory context in SA relevant to services for the care and prevention of CDs. The systematic review of literature on constitutional, legal and regulatory imperatives and the current state of medical genetic services in SA will be conducted by accessing research from journal articles published in peer-reviewed journals. Where required, additional information will be supplemented via personal communication with key individuals and relevant experts.

4.3 Study Design for Research Aim 3: Mapping the burden of CDs in SA

This is an observational, cross sectional study modelling the birth prevalence and outcomes of genetic CDs nationwide in SA over a one-year period. This will demonstrate the national toll of CDs and their contribution to the burden of disease in the country.

The Modell Global Database (MGD) of CDs will be utilised and adapted for the South African context. The MGD was orginally developed in response to a lack of reliable data on national and global birth prevalence of CDs, which is especially lacking in MLIC. It relates known CD prevalence data from well established CD surveillance systems and registries to generate baseline estimates of country-specific birth prevalence [1]. This study develops the MGD a step on from national prevalence estimates by using provincial and district data, when available. This will enable the the regional variations of birth prevalence and outcomes of CDs to be mapped in SA.

4.3.1 Setting

This is a desktop, data analysis study to be undertaken in SA and will involve close collaboration with the originator of the MGD, Prof Bernadette Modell, Emeritus Professor of Community Genetics, University College London and Director, WHO Collaborating Centre for Community Control of Hereditary Disorders.

Demographic data from Statistics SA will be sourced at district and provincial level throughout the country for the latest year it is available (2012 TBC). Due to late registration of births and other demographic data, there is an approximate two-year time lag for these data to be considered complete.

4.3.2 Measurements

The key outcome variable of this study is birth prevalence of early onset genetic CDs. This is the number of infants affected by a CD per 1000 live births in a population and is different from population prevalence, which is the number of individuals affected by a CD in a specific population. Since serious CDs shorten life, population prevalence is usually lower than birth prevalence for CDs, especially in MLIC. Birth prevalence is a more accurate and enables CD rates to be compared across populations and time [1]. The MGD includes CDs causing death or disability in the absence of intervention, namely chromosomal disorders, congenital malformations, single gene disorders and two genetic risk factors, rhesus negativity and G6PD deficiency.

South African provincial and district demographic data will be integrated into the MGD. These demographic data will include: population, annual births, crude birth rate, sex ratio at birth, IMR, U5MR, total fertility rate, mean life expectency, maternal age distribution (% mothers over 35), proportion of the population urbanised, estimated population coefficient of consanguinity and adjusted IMR (if relevant), and population age and sex distribution (Prof. B. Modell, personal communication). Relevant HIV/AIDS data may also be obtained and the IMR adjusted to isolate infant deaths caused by CDs.

4.3.3 Data Analysis

South African demographic data for a specific year will be inputed into the adapted MGD which is in Microsoft Excel. The MGD uses a set of defined methods (using formulae) to relate the demographic data to known birth prevalences of CDs (Prof Bernadette Modell, personal communication). Assistance will be sought from Prof Modell to develop a new formula to adjust the IMR for HIV/AIDS deaths using relevant data sourced from the Health Systems Trust in SA.

Once data input is complete and formulae updated, the MDG will calculate potential (baseline) birth prevalences for which there are a number of possible outcomes. In the absence of any services (i.e. primary prevention and termination of pregnancy), there are four possible outcomes : fetal death/still birth or live birth, which includes death or varying degrees of disability. (primary prevention, termination of pregnancy, fetal death/stillbirth, livebirth, death, disability, and cure). Minimum estimates will be generated for a five year interval.

The results will be described graphically where relevant and published in a relevant peer reviewed journal.

4.4 Study Design for Research Aim 4 & 5: Educational frameworks for undergraduate and post-graduate nursing genetic education and undergraduate medical genetic education.

Development of these educational frameworks are interventional, qualitative studies. A nominal group approach will be employed during a consultative process to achieve consensus on a list of medical genetic competency statements. This approach takes all participants views into account and

can be used for groups of all sizes for decision making while allowing everyone's viewpoints to be taken into consideration. Following consultation with the research group in the UK, this study is based upon the same process used to develop medical genetic core competencies for nurses in the UK [23].

4.4.1 Setting

Development of both of these two frameworks will involve a separate series of meetings of expert panels of a maximum of 40 relevant stakeholders from various health care specialties i.e. South African Nursing Council, South African Medical and Dental Council, HPCSA etc. These meetings will be undertaken at a location/venue to be determined.

4.4.2 Research Object Selection

The project and process will be explained to the potential partner organizations and specific key individuals will be invited to participate, and relevant individuals will be nominated by their organizations to participate. A maximum of 40 stakeholders will participate in each meeting.

Preliminary information will be sent to invited participants explaining the purpose of the study and the role of the educational framework to be developed in contributing to developing capacity required for genetic services in SA.

A list of core competencies developed elsewhere (UK & Europe) will be used as a starting point for discussion. These will be discussed over a 1-2 day meeting to consider the genetics competence required by the healthcare professionals. Where relevant, scenarios may be used within a structured programme and anonymous voting will be undertaken in iterative rounds.

4.4.3 Data Analysis

After the meetings, the agreed statements will be validated against appropriate professional frameworks and refined further, through wider consultation and discussion. The finalized statements will be placed in a framework with proposed learning and practice outcomes. Both the final frameworks and reports will be published in relevant, peer-reviewed journals.

4.5 Study Design for Research Aim 6: A review of medical genetic education in SA- a comparison with the UK

This is an observational, descriptive study. The systematic review of literature on medical genetic education in the UK and SA will be conducted by accessing research from journal articles published in peer-reviewed journals. Descriptions of genetics/genomics content in medical school undergraduate curricula obtained from in-person, informal interviews of relevant teaching staff at key London Medical schools in 2008 and 2014 will also be evaluated. The choice of the UK as a

comparable country is due to the foundations of the SA healthcare system on the UK. As an industrialised country, the UK also completed the epidemiological transition many decades earlier and has had to confront the issue of CDs and develop genetic services and the corresponding genetics education. The study will look at how the state of medical genetics in the UK compared to that of SA when at a similar stage of epidemiological transition, how they transitioned to the current status of education, and what medical genetics education in the UK looks like today. Possible approaches, gaps, lessons learned and a way forward for SA will be evaluated in light of this comparison.

4.6 Study Design for Research Aim 7: The renewed need for care & prevention of CDs in SA: A way forward

This is an observational study. Based on the findings of the previous six papers (Research Aims 1-6) combined with wider desktop research conducted via desktop study of peer reviewed articles, CDs as a health issue in SA and the required services will be contextualized, including genetic education of relevant professionals, will be evaluated. Collectively, this research will provide an evidenced based foundation for generating political will in support of renewed genetic services for the care and prevention of CDs in SA.

5) Ethical Considerations

Informed consent will be obtained from all participants in future interventions of the study. The Biomedical Research Ethics Committee (BREC) at the University of KZN will also be consulted and relevant ethics approval applied for.

6) Time Lines and Project Management

The outputs of this study consist of seven scientific papers that will be submitted for peer review (see Gant Chart attached for further details on timeline):

1. End 2014: Paper 1: Epidemiological transition (BMJ in press, March 2015)
2. First Quarter 2014: Constitutional, legal and regulatory imperatives
3. Second Quarter 2015: The burden of congenital disorders in South Africa (Modell DB)
4. Third Quarter 2015: A review of medical genetic education in SA compared with elsewhere (e.g. the UK)
5. End 2015: Educational framework for undergraduate and post-graduate nursing in SA
6. End 2015: Educational framework for undergraduate medical genetic education in SA
7. Mid 2016: A way forward for the care and prevention of congential disorders in SA

8) Contributors and Authorship

Name	Department	Contribution	Author or acknowledgement
Helen Malherbe	Medicine	Primary Investigator	Author
Colleen Aldous	Medicine	Supervisor	Author
Arnold Christianson	External (NHLS/Wits)	Collaborator	Co-Author
Bernadette Modell	External (University College London)	Collaborator	Co-Author

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Appendix 2: Ethical Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

Amended letter

29 September 2015

Mrs HL Malherbe (212562571)
School of Clinical Medicine
NRMSM
helen@hmconsult.co.za

Dear Mrs Malherbe

Protocol: An investigation into the renewed need for care and prevention of congenital disorders in South Africa.
Degree: PhD
BREC reference number: BF192/15

The Biomedical Research Ethics Committee (BREC) has considered the abovementioned application.

The study was provisionally approved by a meeting of BREC on 09 June 2015 pending appropriate responses to queries raised. Your response dated 06 August 2015 to BREC letter dated 07 July 2015 has been noted by the Biomedical Research Ethics Committee at a meeting held on 08 September 2015. Please take note of the following:

1. PI should acknowledge limitations of the sampling method when discussing analysed data (Query 2).
2. Ethics exemption should have been sought before commencing the study (before publishing 2 review papers). However since the papers used data that is already in the public domain and there is no participant contact, this requirement is condoned.
3. PI and Supervisor should list PI's qualifications which are completed in the CV and not PhD as it is currently in process (Query 9).
4. Supervisor's role should be separated from the Co-PI's roles, this is subject to conflict if the roles are combined (query 10).

This approval is valid for one year from **09 September 2015.** 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 following Committee members were present at the meeting that took place on 09 June 2015:

Prof J Tsoka-Gwegweni	Chair
Dr C Aldous	Genetics
Prof R Bhimma	Paediatrics & Child Health
Rev. S D Chili	External - Lay member
Dr U Govind	Family Medicine
Mr H Humphries	Research Psychology and Public Health
Dr M Khan	Obstetrics and Gynaecology
Prof TE Madiba	General Surgery
Dr T Maistry	External - Microbiology
Prof V Rambiritch	Pharmacology (Deputy Chair)
Prof C Rout	Anaesthetics
Dr A Sathar	External - Microbiology
Dr D Singh	Critical Care
Ms T Van Dou	Legal Member
Prof D Wassenaar	Psychology (Deputy Chair)

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

This approval will be **ratified** at the next BREC meeting to be held on **13 October 2015.**

Yours sincerely

PROFESSOR J Toska-Gwegweni
Chair: Biomedical Research Ethics Committee

cc: Dr C Aldous
cc: Postgraduate Office

Appendix 3: Data Sharing Agreements

UCL CHIME
CENTRE FOR HEALTH INFORMATICS
& MULTIPROFESSIONAL EDUCATION

Helen Louise Malherbe
School of Clinical Medicine
University of Kwa-Zulu Natal
719 Umbilo Road
Congella
South Africa
4013

08 April 2015

Dear Helen,

Re: Modell Global Database – Permission to Use

This letter is to place formally on record that you have my permission to use and adapt data, data structures, techniques and approaches from the Modell Global Database of Congenital Disorders (MGDb) for the purposes of modelling the circumstances prevailing within a country (i.e. South Africa), as outlined in your PhD protocol and discussed with me in detail when we met in London in Autumn 2014.

I wish you every success in this endeavour and look forward to a productive collaboration!

Yours with best wishes,

Bernadette Modell

Professor Bernadette Modell MA PhD MB BChir FRCP FRCOG
Director, WHO Collaborating Centre for the Community Control of Hereditary Disorders

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Enquiries: Kefiloe Masiteng
Reference: Unit records of data
Telephone: 012 310 4663
Email: KefiloeM@statssa.gov.za

STATISTICS SOUTH AFRICA
DATA USER'S AGREEMENT: UNIT RECORDS, MORTALITY AND CAUSES OF DEATH DATA

Statistics South Africa will make available unit record data compiled from death notification forms for the express purpose of calculating age standardized mortality rates.

The Data User must ensure that there is no misuse of the Data or breach of confidentiality and must agree to the following conditions:

1. The User(s) listed in bullet 4 agree that they will not attempt to use, nor permit other to use the data to establish the identity of any person included in any set.

2. The User(s) agree that to keep the Data in a secure environment.

3. The Data may be used only by the named collaborative research team listed in bullet 7 and may not be shared with other Users.

4. The User agrees that any of the Data, or reliance by the User on any of the Data, is at the User's own risk, and that Statistics South Africa shall not be liable for any loss or damage howsoever arising as a result of such use.

5. The use of these Data in research communication, scholarly papers, journals and the like is encouraged, but the authors of these communications and documents agree to acknowledge/cite Statistics South Africa as the source of the Data, making it clear that the analysis and interpretation have been undertaken by the User. The User also agrees to submit to Statistics South Africa a copy of any research publication derived from these Data, for their information.

6. Non-adherence to the above conditions will result in:
    i. Render the User liable for the amount of ZAR 500 000 (Five hundred thousand Rands)
    ii. Statistics South Africa refusing to make available any datasets to the User in future.

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Tel: +27 12 310 8911, Fax: +27 12 310 8500, www.statssa.gov.za, info@statssa.gov.za

7. Signatures of Users:

i. Name: Helen Malherbe
Organisation: University of KwaZulu-Natal & SAIDA
Signature: Helen Malherbe
Signed on: 4 August 2015
Signed at: Fourways, Sandton, Gauteng

ii. Name: Colleen Aldous
Organisation: University of KwaZulu-Natal
Signature: C Aldous
Signed on: 4 August 2015
Signed at: Medical School, UKZN, Durban

iii. Name: Arnold Christianson
Organisation: University of the Witwatersrand
Signature: A Christianson
Signed on: 5th August 2015
Signed at: OAKLANDS, JOHANNESBURG.

iv. Name: Bernadette Modell
Organisation: UNIVERSITY COLLEGE LONDON
Signature: B Modell
Signed on: 4/8/2015
Signed at: 222 EUSTON RD, LONDON NW1 2DA, UK

v. Name: Matthew Darlison
Organisation: UNIVERSITY COLLEGE LONDON
Signature: M Darlison
Signed on: 3/8/2015
Signed at: 222 EUSTON RD, LONDON NW1 2DA, UK

Kefiloe Masiteng
DDG: Population and Social Statistics – Statistics South Africa
Date: 05/08/15