UNIVERSITY OF NAIROBI

THE EPIDEMIOLOGY AND ECONOMIC BURDEN OF MAJOR EXTERNAL STRUCTURAL BIRTH DEFECTS IN KIAMBU COUNTY, KENYA

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University for examination.

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DEDICATION

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ACRONYMS AND ABBREVIATIONS

AIC	Africa Inland Church
ANC	Antenatal Care
CRS	Civil Registration Services
CTEV	Congenital Talipes Equinovarus
DALYs	Disability-Adjusted Life Years
DW	Disability Weights
ETOPFA	Elective Termination of Pregnancy for Foetal Anomaly
EUROCAT	European Surveillance of Congenital Anomalies and Twins
GBD	Global Burden of Disease
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICD-10	International Classification of Diseases 10th Edition
IFAS	Iron-Folic Acid Supplementation
KDHS	Kenya Demographic and Health Survey
KVSR	Kenya Vital Statistics Report
MESBDs	Major External Structural Birth Defects
NBDPN	National Birth Defects Prevention Network
NTD	Neural Tube Defects
PCEA	Presbyterian Church of East Africa
PM	Particulate Matter
SEA	South-East Asia
SDCA	Step-Down Cost Accounting
TRoCA	Tabriz Registry of Congenital Anomalies
WHA	World Health Assembly
WHO	World Health Organization
YLD	Years Lived with Disability
YLL	Years of Life Lost due to premature mortality

OPERATIONAL DEFINITIONS

Admission rate bias/ Berkson bias The concept underlying admission bias is that patients with more than one disease or condition are more likely to be hospitalized than patients with only one disease or condition (Sutton-Tyrrell, 1991).

Ascertainment bias Ascertainment bias occurs when there is inaccurate ascertainment of either the disease or exposure (Sutton-Tyrrell, 1991).

Birth defects Birth defects are defined as abnormalities of body structures or functions, of prenatal origin present at birth, and detectable during pregnancy, at birth, or soon after birth (Sever, 2004; WHO, 2014, 2020).

Confounder A confounder is an extraneous variable that is not in the causal pathway between an exposure and outcome, however, it distorts an association between health exposure and outcome in a population (Hernán, Hernández-Díaz, Werler, & Mitchell, 2002).

Costs Costs are the monetary value of resources used in providing health care services, categorized as direct, indirect, and intermediate costs arising from recurrent, and capital costs (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015; Kirigia, 2009).

Cost analysis Cost analysis is a form of partial economic evaluation entailing identification, measurement, valuation, and comparison of costs of two or more alternatives, however, the effectiveness of alternatives is not compared (Drummond et al., 2015; Kirigia, 2009).

Direct costs Direct costs are the monetary value of all resources used or invested to provide health services such as medical, developmental, and special educational costs (Kirigia, 2009; Waitzman, Romano, & Scheffler, 1994).

Discounting Discounting is the method used to account for individuals' time preferences (McIntosh, 2006).

Indirect costs Indirect costs refer to the monetary value of productive time lost due to participation, or the value of non-medical support in a health program or intervention (Conteh & Walker, 2004; Drummond et al., 2015; Kirigia, 2009; Waitzman et al., 1994).

Intermediate costs	Intermediate costs are the monetary value of medical support or ancillary costs for example laboratory and pharmacy services (Conteh & Walker, 2004).
Final costs	Final costs refer to the summation of total direct, indirect, and intermediate monetary values of the resource inputs for health services (Conteh & Walker, 2004; Drummond et al., 2015; Kirigia, 2009).
Fixed (capital) costs	Fixed (capital) costs refer to the monetary value of resources that do not vary with the quantity of output in the short-term, for example, equipment, vehicles, and buildings (Kirigia, 2009).
Major anomaly	Major anomaly refers to a birth defect with serious adverse effects on health and development, or significant cosmetic effects requiring medical or surgical treatment (Sever, 2004).
Minor anomaly	Minor anomaly refers to a birth defect that does not affect health and development seriously and does not have significant cosmetic effects requiring medical or surgical treatment (Sever, 2004).
Opportunity costs	Opportunity (economic) cost refers to the value of resources in the best alternative use (Cunningham, 2000; McIntosh, 2006).
Overhead costs	Overhead costs refer to the value of resource inputs that are used for more than one program, for example, staff, buildings, vehicles (Kirigia, 2009).
Particulate matter air pollution	This is a mixture of solid and liquid particles varying in number, size, shape, surface area, chemical composition, solubility, and origin suspended in air (Pope III & Dockery, 2006).
Referral bias	Referral bias occurs when the referral patterns specific to a community cause an overrepresentation or underrepresentation of exposed cases in the hospital population as compared to the general population (Sutton-Tyrrell, 1991).
Sensitivity analysis	This is a means of representing uncertainty in the results of economic evaluations (McIntosh, 2006).
Unit cost	These are the costs of providing one good or service and are sometimes referred to as average costs (Conteh & Walker, 2004).

Utility	Utility refers to the value or worth of a given health state or an improvement in that health state valued between zero and one, where zero is equivalent to death and one is equivalent to perfect health (Cunningham, 2000).
Variable (recurrent) costs	Variable (recurrent) costs are defined as the monetary value of resources directly attributed to one intervention or program incurred every year, and often varying with the quantity of output, for example, personnel time, drugs, supplies, nurse or doctor time among others (Kirigia, 2009).

PUBLISHED JOURNAL ARTICLES DRAWN FROM THIS THESIS

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2. Agot, G. N., Mweu, M. M., & Wang'ombe, J. K. (2021). Risk factors for major external structural birth defects among children in Kiambu County, Kenya: a case-control study. *F1000Research, 10* (59). http://dx.doi.org/10.12688/f1000research.50738.2
3. Agot G.N, Wang'ombe J.K, & Mweu M.M, (2021). Cost analysis of outpatient services for major external structural birth defects: An ingredient approach in selected hospitals in Kiambu County, Kenya. *F1000Research, 10* (359). https://doi.org/10.12688/f1000research.52521.1

ABSTRACT

Background: Major external structural birth defects are defined as developmental abnormalities of intrauterine origin that are present at or soon after birth detectable visually during physical examinations and have significant health impacts on the affected children, thus requiring medical and/or surgical interventions. These defects continue to occur globally, however, the greatest burden is shouldered by resource-constrained countries and associated with lifelong resource-intensive physical disabilities exerting enormous financial burden on individuals, and health care systems, nonetheless, they have been unappreciated as a public health priority in Kenya.

Objectives: The broad objective of the study was to determine the epidemiology and economic burden of major external structural birth defects in Kiambu County, Kenya. The specific objectives comprised; (i) to estimate the prevalence of major external structural birth defects, (ii) to identify the risk factors for major external structural birth defects, and (iii) to conduct a cost analysis of outpatient services for major external structural birth defects in the county.

Methods: The study was conducted in 15 hospitals (3 county referral hospitals, 10 sub-county hospitals, and 2 faith-based hospitals within the Kiambu County purposively selected. It is the second-most densely inhabited of the forty-seven counties with an estimated population of 2.4 million of the approximated 47.5 million national population. Approximately 2.2% of its population aged ≥5 years are living with lifelong disabilities associated with congenital anomalies. It is a regional leading commercial hub with agriculture (tea, coffee, and dairy farming) largely as its economic mainstay. The study used two study designs, namely, hospital-based cross-sectional, and hospital-based case-control. First, a retrospective review of all medical records was conducted between January 1st, 2014, and December 31st, 2018, in the 3-county, and 10 sub-county hospitals to estimate the prevalence of the defects. The study enumerated all the cases of birth defects (873) recorded in the medical records in the five years; however, a five-year prevalence numerator of 362 cases was considered following a predetermined inclusion criterion, whereas a five-year prevalence denominator of 299,854 cases of registered live births was obtained from the Birth Registrar. The prevalence estimates were calculated as the number of cases [numerator] divided by the number of live births [denominator]. Associated 95% binomial exact confidence intervals were also computed and expressed per 100000 live births. Secondly, a hospital-based case-control study was conducted in 3 county referral hospitals, 8 sub-county hospitals, and 2 faith-based hospitals to identify the risk factors for the defects. Face-to-face interviewer-structured

questionnaires were administered to 408 study participants [102 cases, and 306 controls] to gather information retrospectively on maternal exposure to environmental teratogens, multifactorial, and sociodemographic-environmental factors during the periconceptional period during their last pregnancies. Logistic regression analyses were conducted to estimate the effects of the predictors on the odds of major external structural birth defects. Lastly, a retrospective review of the outpatient registers for occupational therapy clinics and face-to-face inquiries from occupational therapists were conducted to estimate the unit economic costs of outpatient services for the defects. A one-year time-horizon [January 1st, 2018, to December 31st, 2018] was adopted using ingredient techniques to gather data on the cost drivers from health care providers' perspectives in the county in four hospitals (3 county referral hospitals, and 1 faith-based hospital). The study determined 349 cases following a predetermined inclusion criterion to calculate the unit economic cost in U.S Dollars [$] as the average of the total economic costs divided by the number of cases.

Results: The study showed a steady annual increase in the prevalence estimates of the six groups of major external structural birth defects ranging from 44.04 (95% CI: 27.92-66.07) and 205.28 (95% CI: 173.15-241.64) per 100000 live births between 2014 and 2018**.** Defects of the musculoskeletal system were observed as the most prevalent ranging from 22.98 [95% CI: 11.87-40.13] to 116.9 [95% CI: 92.98-145.08] per 100000 live births between 2014 and 2018. The study further showed women who conceived when residing in Ruiru sub-county [adjusted odds ratio (aOR): 5.28; 95% CI: 1.68-16.58; P<0.01], and Kiambu sub-county [aOR: 0.27; 95% CI; 0.076-0.95; P =0.04]; and preceding siblings with history of birth defects [aOR: 7.65; 95% CI; 1.46-40.01; P =0.02] as the predictors of these defects. The unit economic cost of all the cases was estimated at $ 1,139.73; and $ 1,143.51 for neural tube defects, $ 1,143.05 for congenital talipes equinovarus, and $1,109.81 for congenital pes planus.

Conclusion: This study pointed to an upward prevalence trend in the county between 2014 and 2018 with defects of the musculoskeletal and central nervous systems accounting for the greatest public health and economic burden respectively attributed to genetic and multifactorial factors. Thus, my priority recommendations include the establishment of hospital-based surveillance systems as well as further epidemiological and economic evaluation studies to understand the magnitude of the most prevalent major external structural birth defects in Kenya.

Keywords: Major external structural birth defects, prevalence, risk factors, cost analysis, ingredient techniques, one-year time-horizon, providers' perspective, county, Kenya

CHAPTER ONE: GENERAL INTRODUCTION

1.1 Study background

Major external structural birth defects (MESBDs) are abnormalities of prenatal origin affecting the development of body structures evident before birth, at birth, or soon after and have significant surgical and medical consequences calling for interventions to deal with associated adverse health effects (Christianson, Howson, & Modell, 2005, 2006; WHO, 2014, 2020). Apart from being potentially fatal, these defects have been associated with reduced life expectancy, lifelong physical disabilities, reduced quality of life, and reduced economic productivity among the survivors (Christianson et al., 2005, 2006; WHO, 2014, 2020). Approximately 30% of the birth defects that are clinically obvious and reliably diagnosed around the time of birth in the absence of advanced medical techniques through physical examination of the newborn children include MESBDs among other defects (Modell, Darlison, & Lawn, 2018; Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018; Moorthie, Blencowe, Darlison, Lawn, Mastroiacovo, et al., 2018; Parker et al., 2010; Tinker et al., 2015). The defects are also detectable prenatally through genetic screening, medical imaging, and biochemical analyses of the foetus in utero (Christianson et al., 2005, 2006; Tinker et al., 2015; WHO, 2014, 2020). Synonymously used terms to refer to birth defects include congenital abnormalities, malformations, and congenital anomalies (WHO, 2014, 2020). Thus, these defects can as well be referred to as "major external structural congenital abnormalities, or malformations or anomalies (WHO, 2014, 2020).

The prevalence of MESBDs has been shown to vary from region to region by types and severity attributed to the differences in data drawn either from the hospital or population-based surveillance systems; hospital or population-based epidemiological studies; eligibility criterion including live-births, and/or stillbirths; inaccurate medical records; and unreliable health statistics (Bhide, Gund, & Kar, 2016; Bhide & Kar, 2018; Christianson et al., 2005, 2006; Sever, 2004; WHO, 2014, 2020). The prevalence of these defects has also been noted to vary in the countries without surveillance systems due to the rarity of local epidemiological data and underreporting of the cases by health care systems (Bhide et al., 2016; Bhide & Kar, 2018; Christianson et al., 2005, 2006; Sever, 2004; WHO, 2014, 2020). Public health surveillance systems along with epidemiological studies help define the local epidemiology, recognize emerging cases, detect epidemiological changes, and forewarn health care systems on the existing environmental hazards for birth defects (Moorthie,

Blencowe, Darlison, Lawn, Morris, et al., 2018; Moorthie, Blencowe, Darlison, Lawn, Mastroiacovo, et al., 2018; WHO, 2014, 2020).

MESBDs affect several body organ systems with the most prevalent being talipes equinovarus, Amelia, phocomelia, gastroschisis, and omphalocele affecting the musculoskeletal system; spina bifida, anencephaly, craniorachischisis, and microcephaly affecting the central nervous system; and the cleft lip with or without palate affecting the orofacial structures (Christianson et al., 2005, 2006). The prevalence of birth defects was estimated at 54.33 per 1000 live births in South Korea (Lamichhane et al., 2016), whereas increasing trends of specific proportions of the central nervous system defects, omphalocele, gastroschisis, and orofacial clefts was observed in Ethiopia ranging from 1.14% to 2.83% between 2010 and 2014 (Taye, Afework, Fantaye, Diro, & Worku, 2016). In Tanzania, the prevalence of birth defects was estimated at 60.5 per 1000 live births (Kishimba et al., 2015), whereas the prevalence of major birth defects was estimated at 15.0 per 1000 total births in Kenya (Muga, Mumah, & Juma, 2009).

Worldwide, the public health magnitude of these defects has also been noted to vary credited to the disparate known genetic and environmental factors as well as multifactorial, and sociodemographic factors among women of the reproductive age (Christianson et al., 2005, 2006; Khurmi, Gupta, & Chaudhari, 2014). The defects of genetic etiology have been observed to occur in comparable proportions across the world unlike those of the environmental etiology (Christianson et al., 2005, 2006; WHO, 2013, 2014, 2018, 2020). Notably, the defects of environmental etiology are commonly observed in settings associated with widespread poverty, environmental pollution, sub-optimal prenatal health as well as limited access to family planning, and clinical genetic services by childbearing women beyond 35 years (Christianson et al., 2005, 2006; Gill et al., 2012; Lucas, Stoll, & Bale, 2003; Mashuda, Zuechner, Chalya, Kidenya, & Manyama, 2014; Penchaszadeh, 2002; WHO, 2014, 2020). Factors mediating the intrauterine formation of MESBDs of known genetic etiology consist of single-gene defects, and chromosomal disorders, whereas teratogenic agents are responsible for the formation of MESBDs of known environmental etiology (Christianson et al., 2005, 2006; WHO, 2013, 2014, 2018, 2020). Complex genetic and idiopathic environmental factors on the other hand are known to cause MESBDs of multifactorial etiology, whilst sociodemographic factors include occupation, residence, inadequate

prenatal care, micronutrient deficiencies, and marital status (Christianson et al., 2005, 2006; WHO, 2013, 2014, 2018, 2020).

Although about two-thirds of the causes of MESBDs are not known, around one-third are known to be genetic and environmental-related (Christianson et al., 2005, 2006; Feldkamp, Carey, Byrne, Krikov, & Botto, 2017; WHO, 2014, 2020). Nonetheless, nearly 70% of MESBDs are preventable by modifying the environmental risk factors such as avoiding the teratogens, reproductive years daily intake of folic acid/dietary micronutrients, and periconceptional (between twelve weeks to, and eight weeks after conception) supplementation of iron-folic acid (Botto, Olney, & Erickson, 2004; Christianson et al., 2005, 2006; Feldkamp et al., 2017; Feldkamp et al., 2015; Lucas et al., 2003; Tinker et al., 2015; Toriello, 2005; WHO, 2014, 2020). The supplemental iron and folic acid help to improve the accumulation of maternal serum folate whereas, reduced exposure to the teratogen aids to wean off serum toxins thus reducing mutations of the deoxyribonucleic acid (DNA) causing the intrauterine formation of MESBDs (Botto et al., 2004; Christianson et al., 2005, 2006; Gedefaw, Teklu, & Tadesse, 2018; Lucas et al., 2003; Tinker et al., 2015). Serum folate accumulation plays a significant responsibility in single-carbon transfer reactions and many metabolic pathways including the synthesis of purines and pyrimidines (proteins) underlying the formation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (Manning Feinleib, 2001). Approximately, more than half of pregnancies are unplanned/unintended among women of reproductive age and unrecognized until the end of the first trimester (14 weeks of gestation), whereas first antenatal care (ANC) visits predominantly occur at the end of the second trimester when the defects have already formed within the first eight weeks of gestation (Christianson et al., 2005, 2006; Finer & Zolna, 2014, 2016; KDHS, 2015; Tinker et al., 2015). These observations underscore the public health importance of the periconceptional period as the most opportune time for preventing the occurrence of defects of the environmental etiology (Taye et al., 2016; Tinker et al., 2015).

Substantial resources are known to be always allocated to the surgical and medical care for children born with MESBDs thus exerting an enormous financial burden to the individuals, health care systems, and the society at large (Feldkamp et al., 2017; Feldkamp et al., 2015; Waitzman et al., 1994). In the United States, direct costs of care of major birth defects were estimated at $ 2.6

billion in 2004 (Feldkamp et al., 2017; Mburia-Mwalili & Yang, 2014; Tinker et al., 2015), whereas the cost of lifetime care of an infant born in a single year with at least one major birth defect was approximated to be more than $ 6.0 billion (Ouyang, Grosse, Armour, & Waitzman, 2007). In Germany, the average annual health expenditure of persons with spina bifida was estimated at € 4532, with inpatient health services contributing € 1358 (30.0%), outpatient health services € 644 (14.2%), rehabilitation health services € 29 (0.6%), drug therapy € 562 (12.4%), and other remedies € 1939 (42.8%) (Bowles et al., 2014).

1.2 Statement of the problem

MESBDs continue to occur leading to adverse health consequences and pointing to environmental teratogens, micronutrient malnutrition, and genetic susceptibility among women of reproductive age however they have been neglected, and unappreciated as a public health priority in developing countries (Christianson et al., 2005, 2006; Waitzman et al., 1994; WHO, 2014, 2020). The absence of surveillance systems in addition to epidemiological, and costing studies has contributed immensely to the under-prioritization of MESBDs as a public health problem especially in the developing countries (Mugisha, Kouyate, Dong, & Sauerborn, 2002; Sever, 2004; WHO, 2014, 2020).

The accuracy and completeness of data enumerated during childbirth in Kenya are based on the knowledge and goodwill of the primary health care providers on case definitions and diagnoses. Apart from basic professional training on birth defects, these providers are barely knowledgeable on case definitions, and ascertainment of birth defects thus could lead to misdiagnosis, inaccurate medical records, unreliable health statistics, and underreporting of the cases in the region. They record the information in the maternity files which are designed differently from one hospital to the other with varying fields for entering the names or descriptions of the birth defects. These fields are also inconsistently designed, paged differently, and sometimes missing further leading to undependable health statistics. The information is routinely entered into the maternity registers (MOH333) for hospital reports, and subsequently in the District Health Information System (DHIS) for regional, and national reporting as is the case with other conditions. However, the cases are simply summarised as congenital anomalies in DHIS with no specification of the types, degrees, and regions thus leading to the prevalence underestimation in the country. The absence of national public health surveillance systems, either active or passive compounds the problem

further attributing to inaccurate prevalence numerator data. Nonetheless, this study leveraged accurately defined and/or described cases of MESBDs by the primary health care providers to assemble and analyse the local epidemiological data to understand the extent of MESBDs in Kiambu County.

The foetus develops rapidly in the first eight weeks of pregnancy when most pregnant women in the country are unaware of their pregnancies, not taking folic acid/multivitamins, not attending antenatal clinics, and not on iron-folic acid supplementation due to late antenatal clinic attendance thus potentially exposed to the environmental teratogens unknowingly (KDHS, 2015; Tinker et al., 2015; WHO, 2014, 2020). Therefore, the routine supplementation of iron-folic acid during antenatal care largely serves to improve maternal pregnancy experiences by preventing anemia, puerperal sepsis, low birth weight, preterm births, and not necessarily MESBDs (WHO, 2018). Additionally, unplanned pregnancies, late antenatal care, and exposure to teratogens attributed to socioeconomic and sociodemographic factors such as low levels of education, parental age, teratogen-exposing occupations, as well as the maternal residence at conception could also lead to the occurrence of MESBDs (Kabubo-Mariara, Karienyeh, & Kabubo, 2012; KDHS, 2015; Ochako, Fotso, Ikamari, & Khasakhala, 2011).

The health care systems in developing countries are characterized by unlimited health needs against grossly inadequate resources barely sufficient to meet the populations' health needs underscoring efficient use of the available resources (Drummond et al., 2015; Garber & Phelps, 1997; Kirigia, 2009; Weinstein & Manning, 1997). The national population trends have increased almost five folds over the last five decades from 10.9 million people in 1969 to 47.6 million in 2019 against marginal growth of the health resources perpetuating a disequilibrium of the demand-supply curve of the health services for orthopedic congenital conditions in the region (Kirigia, 2009; KNBS, 2019; Sengupta, 2016). The upward population trajectory along with staggering prevalence trends of MESBDs has also been observed in Kiambu County reported as the second-most densely populated with an estimated population of 2.4 million people of which nearly 2.2% aged ≥5 years are living with lifelong disabilities attributed to MESBDs (KNBS, 2019; Mugoya & Mutua, 2015). Subsequently, considerable resources are constantly allocated to the outpatient occupational therapy services for MESBDs; however their costs and that of the major cost drivers

are not well understood due to the scantiness of local costing data, inaccurately profiled costing data, inadequate costing capacity, and lack of cost analysis studies in the region (Conteh & Walker, 2004; Khurmi et al., 2014; Mugisha et al., 2002).

1.3 Justification and significance of the study

This study endeavoured to determine the epidemiology and economic burden of major external structural birth defects in Kiambu County to provide a snapshot of the public health problem and allow for generalization of the results in similar settings in the region. The estimated public health magnitude could be used to assess the burden of disease, implications of the health services, the performance of health systems, and demonstrate the health needs of the communities, whereas the knowledge on etiological factors could be tailored to formulate risk-based surveillance systems as well as defect-specific preventive and treatment strategies in the region. Similarly, determining maternal genetic susceptibility to birth defects could inform improved access to family planning, and clinical genetic services to childbearing women beyond 35 years and those with histories of birth defects in their families. Additionally, the knowledge on unit economic costs could inform financial budgetary allocations by the county government to the outpatient services for MESBDs. Overall, this study could influence the formulation of policy frameworks for public health prevention and provide a reference point for birth defects surveillance systems, and registries in the region.

1.4 The purpose, objectives, and research questions of this thesis

Overall, this thesis aimed at determining the epidemiology and economic burden of major external structural birth defects in Kiambu County, Kenya. Thus, purposed to contribute to the global epidemiological endeavours, scientific inquiries, and empirical debates on the burden of major external structural birth defects.

The study objectives and research questions are: -

1. To estimate the prevalence of major external structural birth defects from 2014-2018 in Kiambu County. Corresponding questions are: -
    a. What are the frequency distributions of major external structural birth defects from 2014-2018 in Kiambu County?
    b. What are the prevalence estimates of major external structural birth defects from 2014-2018 in Kiambu County?

c. What are the prevalence trends of major external structural birth defects from 2014-2018 in Kiambu County?

2. To identify the risk factors for major external structural birth defects among children in Kiambu County. Corresponding questions are: -
   a. What are the teratogenic risk factors for major external structural birth defects in Kiambu County?
   b. What are the multifactorial risk factors for major external structural birth defects in Kiambu County?
   c. What are the sociodemographic-environmental risk factors for major external structural birth defects in Kiambu County?
3. To estimate the economic costs of occupational and rehabilitative outpatient health services for major external structural birth defects in 2018 in Kiambu County. Corresponding questions are: -
   a. What are the estimated economic costs of occupational and rehabilitative outpatient health services for congenital talipes equinovarus in 2018 in Kiambu County?
   b. What are the estimated economic costs of occupational and rehabilitative outpatient health services for neural tube defects in 2018 in Kiambu County?
   c. What are the estimated economic costs of occupational and rehabilitative outpatient health services for the common major external structural birth defects in 2018 in Kiambu County?

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter entails a comprehensive empirical review and synthesis of literature of the reports, findings, and observations of other studies on MESBDs organized in sections comprising the prevalence, determinants, economic burden, and public health surveillance systems and registries for birth defects.

2.2 Prevalence of major external structural birth defects

The fusion of two haploid gametes (cells) upon conception is the intrauterine stock of foetal health potentially depreciated by endogenous, and exogenous characteristics of women of the reproductive age leading to the formation of MESBDs in utero (Grossman, 1972, 1999). Organogenesis is an intricate highly controlled physiological process coordinated by a network of transcription factors as well as signalling of the molecules and proteins conferring cell polarity and cell-cell interactions occurring rapidly within the eight weeks of gestation (Stanier & Moore, 2004). Thus, maternal exposure to the environmental factors within twelve weeks to conception and eight weeks of conception could cause abnormal intrauterine foetal formation, growth, and development leading to the occurrence of MESBDs in children (Christianson et al., 2005, 2006; Stanier & Moore, 2004; WHO, 2014, 2020). The maternal periconceptional period, therefore, is of great public health significance because of vulnerability to teratogens and appropriateness to effective public health prevention strategies for the defects worldwide (Taye et al., 2016; Tinker et al., 2015). These phenomena can be described as health production functions among women of reproductive age determined by socioeconomic, environmental, and sociodemographic factors as well as physiological profile leading to the occurrence of MESBDs (Grossman, 1972, 1999; Mwabu, 2009; Spencer, 2003; Wagstaff, 1986).

The WHO approximated the total prevalence of birth defects at 472 per 10000 live births for high-income countries, 557 per 10000 live births for middle-income countries, and 662 per 10000 live births for low-income counties (Christianson et al., 2005, 2006; WHO, 2013, 2014, 2018, 2020), whereas the world prevalence was estimated at 397 per 10000 births in 2006 by the March of Dimes (Khurmi et al., 2014). On the other hand, the European Surveillance of Congenital Anomalies and Twins (EUROCAT) which is a population-based public health registry estimated

the overall prevalence of birth defects at 248.6 per 10000 live births between 2010 and 2014 in Europe (Pasha, Vahedi, Zamani, Alizadeh-Navaei, & Pasha, 2017). Similarly, a comparable prevalence of birth defects drawn from population-based data was estimated at 276 per 10000 live births during the same period in the United States (Pasha et al., 2017).

In South Korea, a population-based prevalence study estimated the prevalence of birth defects at 548.3 per 10000 births; 306.8 per 10000 births among boys, and 241.5 per 10000 births among girls between 2009 and 2010 (Lamichhane et al., 2016). In China, the prevalence of birth defects was estimated at 191.84 per 10000 prenatal infants based on surveillance data between 2005 and 2014 in Hunan province (Xie, Yang, Liu, & Wang, 2016), whereas, a similar study based on surveillance data in Guangxi province approximated the prevalence of birth defects at 252.4 per 10000 prenatal infants between 2011 and 2015 (Chen et al., 2018). Additionally, the annual prevalence of structural and functional birth defects was estimated at 690 per 10000 live births in Eastern Mediterranean, and 510 per 10000 live births in South-East Asia (WHO, 2013), whereas the March of Dimes approximated the prevalence of birth defects at 643 per 10000 births in India and ranked it as the 38th most defect-affected country globally (Khurmi et al., 2014).

In Kenya, a hospital-based cross-sectional study conducted at Kenyatta National Hospital in the maternity unit showed defects of the musculoskeletal (33.9%), and central systems (28.6%) as the most frequently occurring MESBDs between 1983 and 1984 (Muga et al., 2009). Additionally, a survey carried out in the same country among under 16 years old children between July 2009 and March 2010 estimated the prevalence of birth defects requiring surgical interventions consisting of spina bifida, imperforate anus, encephalocele, bladder exstrophy, hydrocephalus, hypospadias, clubfoot, and cleft lip at 63 per 10000 children (Wu, Poenaru, & Poley, 2013). In Tanzania, a hospital-based cross-sectional study in four hospitals from October 2011 to February 2012 estimated the birth prevalence of external structural birth defects at 28.3 per 10000 live births (Kishimba, Mpembeni, Mghamba, Goodman, & Valencia, 2015). In Nigeria, a hospital-based cross-sectional study in three hospitals in the Kano metropolis between April 2013 and December 2013 estimated the prevalence of external structural birth defects at 281.5 per 10000 live births

(Anyanwu, Danborno, & Hamman, 2015), whereas in Sudan, the prevalence of birth defects was estimated at 820 per 10000 births in 2006 (Khurmi et al., 2014).

2.3 Environmental causes of major external structural birth defects

The environmental factors causing MESBDs include (i) environmental teratogens and micronutrient malnutrition disrupting the normal intrauterine foetal growth and development, (ii) mechanical factors deforming the foetus in utero, and (iii) vascular accidents interrupting the normal intrauterine growth of the foetal organs (Christianson et al., 2005, 2006; Lucas et al., 2003; WHO, 2014, 2020). Teratogens may be categorized into five groups, namely; (i) physical agents for example radiation (ii) environmental pollutants such as methyl-mercury (iii) maternal illnesses or metabolism disturbance like insulin-dependent diabetes mellitus or iodine deficiency (iv) maternal infections such as rubella, syphilis, and toxoplasmosis; and (v) drugs, both therapeutic and recreational (Christianson et al., 2005, 2006; Lucas et al., 2003). On the other hand, iodine, folate, zinc, riboflavin, and vitamin A are some of the micronutrients required for the normal formation, growth, and development of the foetus in utero whose insufficiency could result in the occurrence of MESBDs (Agbenorku, 2013; Botto et al., 2004; Christianson et al., 2005, 2006).

The environmental teratogens capable of altering the structure of the zygotic deoxyribonucleic acid way before conception or immediately after conception resulting in the intrauterine formation of these defects include pesticides, heavy chemicals, thalidomide, and ionizing radiation agents (Christianson et al., 2005, 2006; Mburia-Mwalili & Yang, 2014; A. G. Mekonnen, Hordofa, Kitila, & Sav, 2020; Modell et al., 2018; Morris et al., 2018; Tinker et al., 2015). Additional teratogens include cigarette smoking, alcohol intake, antidepressants, antiepileptics, congenital maternal infections, hyperthermia, insulin-dependent diabetes mellitus, and obesity (Botto et al., 2004; Ferm & Hanlon, 1983; Hollier, Leveno, Kelly, MCIntire, & Cunningham, 2000; Khoury et al., 1987; Leem et al., 2006; Mlčáková, Hilscherová, & Bláha, 2011; Pašková, Hilscherová, & Bláha, 2011; Sanders et al., 2014; Watkins, Rasmussen, Honein, Botto, & Moore, 2003; Yang et al., 2007). Ambient air pollutants consisting of carbon monoxide, low levels of nitrogen dioxide, oxidized nitrogen, ozone, and particulate components that occur as rough, fine, and very fine particles could also lead to the formation of MESBDs in children (Ritz et al., 2002; Sarigiannis et al., 2017). Suspension or re-suspension of dust, soil, or other thick materials emanating from roads, farming,

volcanoes, sea salts, pollen mould, spores, and other parts of plants parts are known as the rough particles (Chow et al., 2006; Pope III & Dockery, 2006). Fine particles on the other hand are drawn from direct emissions from combustion processes such as gasoline and diesel driven vehicles, wood-burning, coal-burning, smelting, cement plants, paper mills, and steel mills (Pope III & Dockery, 2006; Sarigiannis et al., 2017).

The defects of environmental etiology include - (i) foetal-alcohol spectrum disorders due to maternal alcohol intake, (ii) congenital rubella syndrome, (iii) congenital syphilis (iv) nervous system damage due to insulin-dependent diabetes mellitus; (v) neural tube defects associated with hyperthermia and maternal micronutrient deficiencies; (vi) limb reduction defects associated with thalidomide; (vi) neurological damage related to anticoagulants, organic mercury pollution, and ionizing radiation; and (vii) several birth defects associated with misoprostol and anticonvulsants (Christianson et al., 2005, 2006; Lucas et al., 2003).

2.4 Genetic causes of major external structural birth defects

The intrauterine formation of MESBDs of genetic etiology is attributed to the physiological interactions of the innate parental defective deoxyribonucleic acid leading to pregnancies affected by the defects (Christianson et al., 2005, 2006; Lucas et al., 2003; Sever, 2004; WHO, 2014, 2020). Although the genomic discovery of chromosome microdeletion and single-gene mutations immensely contribute to the understanding of the public health extent of MESBDs of known genetic etiology, the role of complex genetic and idiopathic environmental factors referred to as multifactorial etiology in the intrauterine formation of these defects is yet to be understood across the world (Christianson et al., 2005, 2006; Lucas et al., 2003; Modell et al., 2018; Wellesley, Boyd, Dolk, & Pattenden, 2005; Wellesley, Boyd, Pattenden, & Dolk, 2004; WHO, 2014, 2020). Chromosomal abnormalities have been associated with the occurrence of Down syndrome whereas α- and β-Thalassemia, Sickle cell disorder, and Glucose-6-phosphate dehydrogenase ($G6PD^b$) deficiency have been associated with single-gene defects (Christianson et al., 2005, 2006; Lucas et al., 2003; Pala & Sonvanshi, 2016; Stanier & Moore, 2004).

The sex of the ‘last-born’ (current) child, siblings with a history of birth defects, familial history of birth defects, parity (primiparous, and multiparous), nature of gestation (single and multiple),

race, ethnicity, and parental age are some of the factors associated with the defects of genetic (known and complex), and environmental (known and idiopathic) etiology (Bray, Gunnell, & Smith, 2006; Cui et al., 2005; Fraser, Brockert, & Ward, 1995; Hollier et al., 2000; Lamichhane et al., 2016; Ouyang et al., 2007). The defects associated with the above-mentioned etiological factors include congenital talipes equinovarus, hip dysplasia, phocomelia, and Amelia affecting the musculoskeletal system; anencephaly, spina bifida, hydrocephalus, and encephalocele affecting the central nervous system; cleft lip and cleft palate affecting orofacial structures; and epispadias, and hypospadias affecting the male genital organs (Allagh et al., 2015; Christianson et al., 2005, 2006; Gedefaw et al., 2018; Lucas et al., 2003; Stanier & Moore, 2004; Tanriverdi, Delibas, Kamalak, Kadioglu, & Bender, 2015; WHO, 2014, 2020).

Although MESBDs of genetic origin are fatefully bound to occur, sufficient access to and utilization of family planning and clinical genetic services by women of advancing childbearing age beyond 35 years and those with a positive familial history could help in preventing the occurrence of these defects in the region (Christianson et al., 2005, 2006; Feldkamp et al., 2017; Feldkamp et al., 2015; Lucas et al., 2003; Tinker et al., 2015). Some of the clinical genetic services aimed at preventing the occurrence of the defects acquired genetically include genetic counselling, prenatal diagnosis, related treatment, and elective termination of pregnancies for foetal anomalies in the jurisdictions with favourable legislative frameworks (Christianson et al., 2005, 2006; WHO, 2014, 2020). Further epidemiological studies are also required to unravel the mystery underlying the mechanisms of actions of the idiopathic environmental and complex genetic factors in the causation of MESBDs to inform public health actions in preventing the occurrence of defects of multifactorial etiology (Botto et al., 2004; Feldkamp et al., 2017; Feldkamp et al., 2015; Gedefaw et al., 2018; KDHS, 2015; Lucas et al., 2003; Tinker et al., 2015).

2.5 Sociodemographic-environmental and major external structural birth defects

The environmental factors are also known to act through socioeconomic and sociodemographic characteristics of the women of reproductive age to cause the intrauterine formation of MESBDs thus described as sociodemographic-environmental etiological factors (Christianson et al., 2005, 2006; Spencer, 2003). The socioeconomic factors such as education, occupation (income), and poverty, whereas sociodemographic factors comprise residence, parental age, ethnicity/race, residence, marital status, and consanguineous marriages known to influence maternal exposure to

teratogens and micronutrient deficiencies (Bray et al., 2006; Christianson et al., 2005, 2006; Grossman, 1972; Hollier et al., 2000; Kabubo-Mariara et al., 2012; Lucas et al., 2003; Spencer, 2003; Wagstaff, 1986; Wilkinson & Marmot, 2003; Yang et al., 2007). Women with high levels of education are likely to make informed decisions during market (economic) and non-market (leisure) activities in quest for good health because of their ability to comprehend health information and to pay for health services compared to those with low levels of education (Fraser et al., 1995; Grossman, 1972, 1999; Ochako et al., 2011; Wagstaff, 1986). However, educational levels would also attract women to occupations such as farming that would otherwise expose them to chemicals and heavy metals from farm-sprayed pesticides if the protective equipment is not used appropriately leading to the occurrence of MESBDs (Mlčáková et al., 2011; Pašková et al., 2011).

The age of parents, on the other hand, is a multidimensional predictor whose modes of actions in the occurrence of MESBDs are underpinned by human biology and socioeconomic characteristics of women of reproductive age (Bray et al., 2006; Christianson et al., 2005, 2006; Florentina Mashuda, 2014; Fraser et al., 1995; Hollier et al., 2000). Human biology is also manifold in its mechanisms attributed to abnormal oogenesis (female gametogenesis) and spermatogenesis (male gametogenesis) due to advancing parental age beyond 35 years (Bray et al., 2006; Florentina Mashuda, 2014). Firstly from the biological viewpoint, oogenesis begins in the foetus before birth with the initial meiotic division normally completed shortly before ovulation, however, sometimes the division takes up to 45 years thus increasing the likelihood of meiotic errors due to the oocytes being exposed to environmental teratogens as a result of prolonged initial meiotic division (Florentina Mashuda, 2014). Additionally, many women who are childbearing beyond 35 years increase the likelihood of defect-affected pregnancies due to chromosomal abnormalities (Florentina Mashuda, 2014; Moore, Persaud, & Torchia, 2018; Shawky & Sadik, 2011).

Meiotic errors during oogenesis may also lead to chromosomal abnormalities including Down's syndrome, Edward's syndrome, and Patau's syndrome (Feldkamp et al., 2017; Feldkamp et al., 2015; Florentina Mashuda, 2014). Notably, Down syndrome (trisomy 21) occurs as a result of an extra 21st chromosome in the foetus causing characteristic physical features, short statures, and developmental infirmities; three copies of chromosome 18 are referred to as Edward's syndrome

(trisomy 18) potentially causing lethal medical and developmental ramifications during and beyond infancy; whereas three copies of chromosome 13 are known as Patau's syndrome (trisomy 13) causing deadly facial and skull anomalies such as brain anomalies, cleft lip, and cleft palate as well as developmental delays (Feldkamp et al., 2017; Feldkamp et al., 2015). Secondly from the biological perspective, spermatogenesis characterized by genetic mutations and accumulation of chromosomal aberrations during maturation of the male germ cells similarly contributes to the occurrence of MESBDs (Barker, Chesney, Miedzybrodzka, & Maffulli, 2003; Bray et al., 2006; Christianson et al., 2005, 2006). The amount of deoxyribonucleic acid damage has been observed to be three times in sperm of men aged 36-57 similarly increasing the likelihood of MESBDs occurring in children whose parents are aged more than 35 years (Bray et al., 2006; Yang et al., 2007).

Socioeconomic characteristics including education, poverty, and occupation could also influence environmental hygiene, parity, conception planning, gestational age at first antenatal visit, and trimester antenatal care begins thus stimulating dietary micronutrient intake, and iron-folic acid supplementation among women of reproductive age as measures aimed at preventing MESBDs (Christianson et al., 2005, 2006; Finer & Zolna, 2014, 2016; Freitas, Nunes, Meneguci, Nascimento Neto, & Castro, 2021; Kabubo-Mariara et al., 2012; Tinker et al., 2015). Although marital status and consanguineous marriage are some of the sociodemographic predictors, they are largely associated with defects of the genetic etiology as a result of the physiological interactions of deoxyribonucleic acid variants between the partners (Bello, Acquah, Quartey, & Hughton, 2013; Christianson et al., 2005, 2006).

2.6 Epidemiology and burden of musculoskeletal system defects

Birth defects of the musculoskeletal system are a group of diverse congenital anomalies involving the bones and muscles; bones constitute the human skeleton adjoined by tendons, ligaments, cartilages, muscles, and other connective tissues (Sever, 2004; WHO, 2014, 2020). Worldwide, the most frequently occurring MESBDs are accounted for by the defects of the musculoskeletal system including gastroschisis, omphalocele, congenital talipes equinovarus, Amelia, and phocomelia, among other defects (WHO, 2014, 2020). Gastroschisis is a defect of the anterior abdominal wall characterized by an opening anterior to the umbilicus accompanied by protrusion

of the small intestines, parts of the large intestines, and sometimes organs of the abdomen such as the liver and spleen (Chabra & Gleason, 2005; Sever, 2004; WHO, 2014, 2020). Omphalocele is also a defect of the anterior abdominal wall characterized by protrusion of abdominal contents/organs (intestines and/or spleen and liver) through an enlarged umbilical ring and the umbilical cord inserted in the distal part of the membrane covering the defects (Sever, 2004; WHO, 2014, 2020). In omphalocele, the widened umbilical cord allows protrusion of abdominal organs, small intestines, parts of the large intestines, and occasionally the liver and spleen into the umbilical cord (Sever, 2004; WHO, 2014, 2020).

Gastroschisis and omphalocele are among the exceedingly rare defects of the musculoskeletal system, however, they are noted as the most prevalent defects of the anterior abdominal wall muscles and attributed to periconceptional obesity and overweight (Chabra & Gleason, 2005; Watkins et al., 2003; WHO, 2014, 2020). Although these defects are mostly incompatible with survival, prolonged hospitalizations have been observed among children with gastroschisis surviving beyond infancy due to intestinal dysfunctions and feeding intolerance (Hook-Dufresne, Yu, Bandla, Imseis, & Moore-Olufemi, 2015). Worldwide, the average length of hospital stay for children born with gastroschisis was reported to vary between 37.6 days in 2007 and 39.4 days in 2011 hence associated with substantial financial burdens to the individuals and health care systems (Hook-Dufresne et al., 2015).

Congenital talipes equinovarus is also a defect of the musculoskeletal system in which the Achilles tendon is partially or completely disrupted above the heel of the newborn child (T. Smythe, H. Kuper, D. Macleod, A. Foster, & C. Lavy, 2017). Although it affects the structures and positions of the foot leading to a twisted foot and preventing the sole from being flatly placed on the ground, they are compatible with life (Tracey Smythe, Hannah Kuper, David Macleod, Allen Foster, & Christopher Lavy, 2017; WHO, 2014, 2020). Gender, maternal smoking as well as positive familial and siblings history of birth defects are some of the factors associated with congenital talipes equinovarus (Pavone et al., 2012). It is characterized by lifelong resource-intensive physical disabilities, chronic pain, impaired mobility, participation restrictions, and activity limitations among the affected children (Tracey Smythe et al., 2017; Theologis, Harrington, Thompson, &

Benson, 2003). Limb reduction defects on the other hand comprise deformities of upper and lower limbs with the upper limb defects consisting of complete absence (Amelia) or partial absence (Phocomelia) of the upper arm/humerus, lower arm/radius and/or ulna, wrist/carpals, hand/metacarpals, or fingers/phalanges (Sever, 2004). Lower limb defects also include complete absence (Amelia) or partial absence (Phocomelia) of the upper leg/femur, lower leg/tibia and/or fibula, ankle/tarsals, foot/metatarsals, or toes/phalanges (Sever, 2004).

Maternal use of statins (lipid-lowering therapeutic medicines) for example simvastatin 20mg/day between 0-6 weeks after the lost menstrual period during the first month of gestation, and concomitant use of aspirin, codeine, acetaminophen, propoxyphene has also been associated with the defects of the musculoskeletal system (Edison & Muenke, 2004). Maternal use of simvastatin 10mg/day between 0-13 weeks after the lost menstrual period and concomitant use of progesterone (10 days/month) has specifically been associated with the left femur 16% shorter than the right side, failure of the left foot to form, as well as second, third, and fifth toes (Edison & Muenke, 2004). Right fibula and tibia 9% shorter than the left side (Phocomelia), lack of one ankle bone (Amelia), and right foot 16% shorter than the left side (Phocomelia) have been mostly observed in children at 4 years of age (Edison & Muenke, 2004). Maternal exposure to thalidomide has also been associated with the occurrence of limb reduction defects such as Amelia and phocomelia in children (Mburia-Mwalili & Yang, 2014; Modell et al., 2018; Morris et al., 2018).

2.7 Epidemiology and burden of defects of the central nervous system

Defects of the central nervous system, also referred to as neural tube defects (NTD) are a group of defects that affect the developing brain and spine occurring when the neural tube either fails to form or close correctly or completely at the sacral, cervical, thoracic or lumbar vertebrae within 28 days of gestation (Gedefaw et al., 2018; Toriello, 2005). They consist of anencephaly, spina bifida, encephalocele, iniencephaly, and craniorachischisis among other defects (Gedefaw et al., 2018; Toriello, 2005). Spina bifida is the failure of the posterior vertebral arches to close over neural tube exposing the spine and nerve often located in the lumbar or sacral vertebrae (Edison & Muenke, 2004; WHO, 2014, 2020). Spina bifida is usually compatible with survival, however, it may lead to lifelong physical disabilities, mental retardation, and adverse psychological effects

among the affected individuals (Kronenberger & Thompson Jr, 1992; Toriello, 2005; Wallander, Feldman, & Varni, 1989).

Anencephaly on the other hand is the partial or complete absence of the brain, cranial vault, and the covering skin, whereas encephalocele is a sac-like protrusion of the brain and/or its membranes through the skull often occurring in the occipital region (Toriello, 2005; WHO, 2014, 2020). Craniorachischisis is an anencephaly accompanied by a contiguous spinal bony defect exposing the neural tissues and meninges (Tanriverdi et al., 2015; Toriello, 2005; WHO, 2014, 2020). Iniencephaly is characterized by a closed cranium, short spinal column rotation, retro-flexion of the head, and absence of the neck (Tanriverdi et al., 2015; Toriello, 2005; WHO, 2014, 2020). Even though anencephaly is largely incompatible with life and associated with prenatal fatalities unlike spina bifida, they constitute the most common forms of central nervous system defects worldwide (Toriello, 2005). Conversely, even though iniencephaly and craniorachischisis are also incompatible with life unlike encephalocele, they comprise some of the rarest forms of central nervous system defects globally (Tanriverdi et al., 2015; Toriello, 2005; WHO, 2014, 2020). Worldwide, anencephaly, spina bifida, and encephalocele account for more than 90% of the defects of central nervous systems (Bowles et al., 2014; Hage, Jalloul, Sabbah, & Adib, 2012; Nasr & Abi, 2012; WHO, 2014, 2020).

The prevalence of the defects of the central nervous system was estimated at 5-20 per 10000 pregnancies accounting for the highest-burden of disease associated with MESBDs across the world (Fischer, Stronati, & Lanari, 2017), with the prevalence of non-syndromic spina bifida estimated at 4.71 per 10000 births, and non-syndromic encephalocele at 1.12 per 10000 births between 2005 and 2010 (Bowles et al., 2014). On the other hand, the prevalence of Iniencephaly was estimated to vary between 0.1 to 10 per 10000 pregnancies commonly occurring among girls usually associated with high prenatal and early neonatal fatality rates (Tanriverdi et al., 2015). In Kenya, a population-based study conducted between 2009 and 2010 estimated the prevalence of hydrocephalus at 9 per 10000 children followed closely by spina bifida at 5 per 10000 children, and encephalocele at 4 per 10000 children (Wu et al., 2013). Additionally, a hospital-based cross-sectional study at the maternity unit of Kenyatta National Hospital in the same country estimated

the prevalence of defects of the central nervous system at 49 per 10000 births accounting for 28.6% of MESBDs between 1983 and 1984 (Muga et al., 2009). A hospital-based cross-sectional study was also conducted on congenital anomalies that presented for surgical interventions including spina bifida, encephalocele, clubfoot, and hydrocephalus between 2005 and 2010 at Kijabe AIC hospital in Kenya (Githuku et al., 2014). The study estimated an overall prevalence of spina bifida and encephalocele at 3.3 per 10000 live births during the study period and noted that in 2007 spina bifida and encephalocele accounted for the highest-burden of disease estimated at 4.4 per 10000 live births (Githuku et al., 2014).

In Khartoum Sudan, a hospital-based cross-sectional study at two hospitals estimated the prevalence of central nervous system defects at 28 per 10000 births (Omer, Abdullah, Mohammed, & Abbasher, 2016), whereas, a hospital-based cross-sectional study in four hospitals in Tanzania between October 2011 and February 2012 showed central nervous system defects as the most prevalent at 9.9 per 10000 live births mostly affecting the female children and contributing more than 50% perinatal deaths (Kishimba, Mpembeni, Mghamba, et al., 2015). Hydrocephalus which is a defect of the central nervous system characterized by accumulation of fluid inside the cranium and swelling of the brain usually associated with other forms of central nervous system defects was also observed in the same study mostly among males in Tanzania (Kishimba, Mpembeni, & Mghamba, 2015).

In South Korea, a population-based prevalence study carried out between 2009 and 2010 showed that defects of the central nervous system were the third most prevalent estimated at 15.6 per 10000 births (Lamichhane et al., 2016). Defects of the musculoskeletal systems were however observed as the most common estimated at 105.7 per 10000 births followed by those of the digestive systems at 24.7 per 10000 births during the same period in South Korea (Lamichhane et al., 2016). In Iran, the prevalence of defects of the central nervous system was estimated at 320 per 10000 births, and 40 per 10000 total births in India (Allagh et al., 2015; Pasha et al., 2017), whereas spina bifida was approximated at 20 per 10000 births in America (Young, Sheridan, Burke, Mukherjee, & McCormick, 2013).

The risk factors associated with defects of the central nervous include micronutrient deficiency, hyperthermia, poverty, low parity, overweight, severe obesity, insulin-dependent diabetes mellitus, sulphonamides, tetracycline, antihistamine, statins, and antitumor agents (Anyanwu et al., 2015; Bowles et al., 2014; Edison & Muenke, 2004; Hage et al., 2012; Hage & Rizk, 2012; Nasr & Abi, 2012; Rofail, Maguire, Kissner, Colligs, & Abetz-Webb, 2014; Tanriverdi et al., 2015; Watkins et al., 2003). Lovastatin 20mg/day which is a lipid-lowering agent when administered with no concomitant medications or illness has also been associated with the occurrence of defects of the central nervous system, whereas insulin-dependent diabetes mellitus, atorvastatin (statin), and severe obesity with a body mass index (BMI) greater than $30kg/m^2$ have specifically been associated with spina bifida (Edison & Muenke, 2004; Watkins et al., 2003; WHO, 2014, 2020).

The closure of the neural tube occurs within four weeks (28 days) of gestation long before the unplanned/unintended pregnancies are recognized compounding the high prevalence of defects of the central nervous system (Tinker et al., 2015; Toriello, 2005). Daily administration of 400 to 5000µg (0.4-5mg) folic acid recommended for women throughout their reproductive life, at least four weeks before conception and throughout the first trimester has been shown to reduce incidences of defects of the central nervous system by 40% to 80% in women with or without prior history of the defects (Bowles et al., 2014; Hage et al., 2012; Hage & Rizk, 2012; Nasr & Abi, 2012; Tinker et al., 2015; Toriello, 2005). Daily oral supplemental elemental iron of 30mg-60mg and folic acid 0.4mg during the periconceptional period have also been noted to prevent more than 70% of the central nervous system defects including orofacial clefts, cardiac and renal anomalies (WHO, 2018).

Substantial healthcare expenditures have been associated with life-compatible forms of central nervous system defects during infancy, childhood, and adulthood because of the effective interventions including surgical repairs, rehabilitative services, and lifelong care (Bowles et al., 2014; Christianson et al., 2005, 2006; Waitzman et al., 1994). In Germany, a retrospective analysis of health insurance data was conducted to determine the economic burden of illnesses associated with neural tube defects based on the International Classification of Diseases, 10^{th} Edition (ICD-

10) codes (Bowles et al., 2014). The study observed that age group-specific stratified analysis of outpatient and inpatient care, remedies and aids, pharmacotherapy use, long-term care, and information on sick leave showed substantial economic costs throughout life were mainly associated with spina bifida (Bowles et al., 2014). The study further reported that the average annual health expenditures of persons with spina bifida were estimated at € 4532, with inpatient care contributing € 1358 (30.0%), outpatient care € 644 (14.2%), rehabilitation € 29 (0.6%), pharmacotherapy € 562 (12.4%), and remedies and medical aids € 1939 (42.8%) in Germany (Bowles et al, 2014). The economic burden of spina bifida remains enormous throughout one's life, with high health care expenditures experienced during the early years of life (Bowles et al., 2014). Additionally, another study observed that the estimated average lifetime direct medical costs per person with spina bifida ranged between $ 285,959 and $ 378,000 in 2010 across the world (Rofail, Maguire, Kissner, Colligs, & Abetz-Webb, 2013).

In the United States, children aged between 1-17 years with spina bifida were estimated to spend 13 times greater on medical expenditures than children without spina bifida between 2001 and 2003 (Ouyang et al., 2007). A human capital method was also used to compute direct costs of illnesses consisting of medical, developmental, and special education costs, and indirect costs comprising lost work and hospital productivity due to premature deaths associated with the clinically important structural congenital anomalies in the United States in 1992 (Lary & Edmonds, 1996, 1997). This study estimated the direct costs of spina bifida at $ 294,000 million and lifetime costs that included developmental costs at $ 489 million (Lary & Edmonds, 1996, 1997), whereas spina bifida reportedly accounted for the highest-burden of the disease ranging from 106-234 DALYs in a population-based study conducted between 2009 and 2010 in Kenya (Wu et al., 2013).

2.8 Epidemiology and burden of orofacial clefts

Orofacial clefts occur when the facial primordial/prominence fails to meet and fuse/form the appropriate features during intrauterine development of the fetal head (Stanier & Moore, 2004). This failure results in malformations of the structures around the oral cavity extending into the facial structures (craniofacial deformities) consisting of clefts of the lip and/or palate (CL/P) (Agbenorku, 2013; Pala & Sonvanshi, 2016). Cleft palate (CP) is an inappropriate formation occurring on the roof (hard palate) of the mouth and the soft tissues (soft palate) at the back of the

mouth, whereas, cleft lip (CL) is inappropriate development of the lip structures (Agbenorku, 2013; Pala & Sonvanshi, 2016).

The etiological factors associated with orofacial clefts include chromosomal abnormalities, single gene defects, severe maternal obesity, maternal overweight, infections, alcohol consumption, cigarette smoking, retinoic acid, anticonvulsants, and prenatal nutritional vitamin B6, and folate deficiencies (Agbenorku, 2013; Conway et al., 2015; Hackshaw, Rodeck, & Boniface, 2011; Pala & Sonvanshi, 2016; Stanier & Moore, 2004; Watkins et al., 2003). Approximately 70% of the CP occur singularly thus referred to as non-syndromic because they occur as isolated defects and are considered etiologically distinct from CL and/or CP (Stanier & Moore, 2004). The remaining orofacial clefts on the other hand are described as syndromic because they occur associated with chromosomal abnormalities, Mendelian single-gene syndromes, teratogens, and unknown syndromes (Stanier & Moore, 2004). Chromosomal microdeletion has also been associated with the occurrence of non-syndromic orofacial defects (Stanier & Moore, 2004), whereas nutritional zinc deficiency has been associated with isolated CP (Agbenorku, 2013; Modell et al., 2018; Taye, Afework, Fantaye, Diro, & Worku, 2018, 2019).

Worldwide, CL/P are among the most common MESBDs with prevalence estimated between 1 per 300 to 1 per 2500 births for CL and/or without CP, and 1 per 1500 births for CP (Agbenorku, 2013; Onyango & Noah, 2005; Stanier & Moore, 2004). Approximately 50% of CL occurs with CP associated with the secondary effects resulting from CL during the fusion of facial prominence that preceded the formation of the palate (Stanier & Moore, 2004). Orofacial clefts have been reported to affect males more than their female counterparts in the ratio of 3:2 (Agbenorku, 2013; Pala & Sonvanshi, 2016; Stanier & Moore, 2004). Similarly, CL and CP do occur concurrently more frequently in males compared to females whereas CL and CP tend to occur separately (Agbenorku, 2013; Pala & Sonvanshi, 2016; Stanier & Moore, 2004). Approximately half of the CL and CP have been noted to occur together and their prevalence is reported to vary by geographical locations, race, and ethnicity (Agbenorku, 2013; Pala & Sonvanshi, 2016; Stanier & Moore, 2004). Orofacial clefts are common in children of Asian, Latino, and Native American descent, however, the risk is relatively greater among the Asians than other regions estimated to

occur at 14 per 10000 births followed by Whites at 10 per 10000 births, and African Americans at 4 per 10000 births (Agbenorku, 2013). It was observed in the United States that CL and/or CP were the fourth most common congenital anomaly affecting 1 per 700 babies yearly (Agbenorku, 2013). In Iran, the prevalence of orofacial clefts was estimated at 14 per 10000 births (Pasha et al., 2017), whereas the overall prevalence of orofacial clefts was estimated at 13 per 10000 total births in India (Allagh et al., 2015).

The prevalence estimates of orofacial clefts have also been noted to vary in Africa approximated at 3 per 10000 live births in Nigeria, 9 per 10000 live births in Sudan, and 50 per 10000 live births in Gambia (Agbenorku, 2013). A hospital-based study between 2000 and 2003 estimated the prevalence of orofacial clefts at 16.5 per 10000 live births in Kenya (Onyango & Noah, 2005), whereas a population-based study between 2009 and 2010 estimated the prevalence of CL at 4 per 10000 in Kenya (Wu et al., 2013). In Kenya, syndromic CL and CP were observed as the most common orofacial clefts followed by isolated (non-syndromic) CL and CP, whereas males were noted as the most affected by the orofacial clefts compared to their female counterparts and commonly occurring on the left side of the mouth (Onyango & Noah, 2005). In Tanzania, a cross-sectional study conducted in four hospitals between October 2011 and February 2012 also observed orofacial defects to occur mostly among the males (Kishimba, Mpembeni, & Mghamba, 2015).

Orofacial clefts are associated with significant clinical consequences often requiring multiple surgeries and medical treatments including speech therapy, and psychological treatments during childhood hence associated with the substantial economic burden to individuals and health care systems (Boulet, Grosse, Honein, & Correa-Villaseñor, 2009; Stanier & Moore, 2004; Waitzman et al., 1994). Data drawn from privately insured U.S populations between 2000 and 2004 that analyzed expenditures for inpatient admissions, outpatient health services, and prescription drug claims for children aged between 0 and 10 years with or without orofacial clefts showed staggering annual costs approximated at $ 13,405 (Boulet et al., 2009). The same study showed that the mean and median costs for children ≤ 10 years of age with an orofacial cleft were eight times higher than for children of the same age without an orofacial cleft (Boulet et al., 2009). Further, the mean costs

for infants with an orofacial cleft and another major unrelated defect were estimated at 25 times higher than those for an infant without an orofacial cleft, and five times higher than for infants with an isolated orofacial cleft (Boulet et al., 2009). The study consequently showed that the costs of orofacial clefts were substantially elevated for privately insured children that otherwise would be catastrophic to the health care systems if the study considered the providers' economic perspectives rather than payers' perspectives (Boulet et al., 2009). This could be attributed to distortions in the health market characterized by moral hazard, adverse selection, and information asymmetry among health service consumers (Garber & Phelps, 1997; Peter Zweifel, 1997). However, DALYs associated with orofacial clefts have been observed as the lowest compared to other defects estimated between 3.5 to 7.7 from 2009 to 2010 based on a population study in Kenya (Wu et al., 2013).

2.9 Epidemiology and burden of other major external structural birth defects

The presence of some of the exceedingly rare major or minor external structural birth defects is of similar public health importance because sometimes they point to latent major internal birth defects that could manifest clinically later in a lifetime or be diagnosed using advanced medical imaging techniques (Parker et al., 2010; Romitti, 2007; Sever, 2004). Similarly despite being rare, these defects are of great significance because of the associated multiple aetiologies with other latent major external/internal structural birth defects, substantial economic resources as well as long-term adverse health and psychological effects (Lund et al., 2009; van der Horst & de Wall, 2017). Such defects include hypospadias, epispadias, imperforate anus, syndactyly, polydactyly, and microtia (Christianson et al., 2005, 2006; Lund et al., 2009; Parker et al., 2010; Romitti, 2007; Sever, 2004; van der Horst & de Wall, 2017; WHO, 2014, 2020). The prevalence of hypospadias which is a defect of the male genital organ was estimated at 9.0 per 10000 live births from population-based data, whereas the prevalence of imperforate anus was estimated at 2 per 10000 live births in the same study between 2009 and 2010 in Kenya (Wu et al., 2013).

2.10 Economic burden of major external structural birth defects

The resource inputs for providing outpatient care for MESBDs are substantial and continue to exert an enormous economic burden on families and health care systems unless they are effectively prevented from occurring (Bowles et al., 2014; Conway et al., 2015; Drummond et al., 2015; Waitzman et al., 1994). MESBDs require appropriate treatments to increase childhood survival

and improve the quality of life, life expectancy, as well as economic productivity of the affected individuals (Bowles et al., 2014; Christianson et al., 2005, 2006; Sengupta, 2016; Sitkin, Ozgediz, Donkor, & Farmer, 2015; Waitzman et al., 1994). Tenotomies, castings, bracings, physical and developmental therapies are some of the effective, and efficient interventions commonly available for orthopedic congenital conditions whose burden could be determined by economic evaluation studies (Drummond et al., 2015; Kirigia, 2009). The studies are classified as partial methods valuing only the costs of at least two alternative health interventions; and full methods valuing both costs and consequences of at least two alternative health interventions (Drummond et al., 2015; Kirigia, 2009).

Cost analysis is an example of a partial economic evaluation, however, it is still useful for measuring the costs of a single health intervention even in the absence of alternative interventions to estimate its burden based on average unit economic costs (Birch & Gafni, 1996; Briggs, Sculpher, & Buxton, 1994; Drummond et al., 2015; Kirigia, 2009; Mogyorosy & Smith, 2005). On the other hand, full economic evaluation methods include cost-effectiveness, cost-benefit, and cost-utility analyses that measure the burden associated with the interventions based on marginal economic costs (Birch & Gafni, 1996; Briggs et al., 1994; Drummond et al., 2015; Kirigia, 2009; Mogyorosy & Smith, 2005). The costs of the health interventions are measured by economic evaluation studies in monetary units, whereas, consequences are measured in natural units including life-years gained, and disability-days saved in cost-effectiveness analysis; and healthy years measured as quality-adjusted life years, and disability-adjusted life-years in cost-utility analysis (Drummond et al., 2015; Kirigia, 2009). Notably, costs and consequences of health interventions are both measured in monetary units only in cost-utility analysis underpinning the welfare economic theories on the burden associated with MESBDs from societal perspectives (Drummond et al., 2015; Kirigia, 2009; Mogyorosy & Smith, 2005).

The economic evaluation studies are carried out from individuals', providers', payers' and societal perspectives determined by the policy decisions to inform the study objectives and questions subsequently defining the range, contexts, and extents of the cost elements of the economic evaluation activities (Conteh & Walker, 2004; Drummond et al., 2015; Kirigia, 2009; Mogyorosy

& Smith, 2005). The study questions consider: - (a) which costs should be considered? (b) how should the costs be estimated? (c) and how accurate should the costs be estimated? (Drummond et al., 2015; Kirigia, 2009). These studies are useful in informing health planning, policy decisions, resource allocations, health system performance assessments, and further economic studies in similar settings (Birch & Gafni, 1996; Briggs et al., 1994; Conteh & Walker, 2004; Cunningham, 2000; Sandmann, Robotham, Deeny, Edmunds, & Jit, 2018).

Substantial resources are known to be allocated to the health services for these defects, however, their economic costs and that of the major cost drivers are not well understood in developing countries (Conteh & Walker, 2004; Khurmi et al., 2014; Mugisha et al., 2002; Parker et al., 2010). The resources are categorized as direct medical costs, direct non-medical costs, and indirect medical costs with direct medical costs being the monetary value of the remedial inputs including pharmacy, laboratory, radiology, and medical consumables used to provide health services (Conteh & Walker, 2004; Drummond et al., 2015; Kirigia, 2009; Waitzman et al., 1994). Direct non-medical costs are the value of resources incurred as a result of the long-term effects of the defects including developmental, and special educational costs (Conteh & Walker, 2004; Drummond et al., 2015; Kirigia, 2009; Waitzman et al., 1994). On the other hand, indirect medical costs are the monetary value of lost work and productivity time of the individuals, caregivers, and providers due to premature deaths or illnesses (Conteh & Walker, 2004; Drummond et al., 2015; Kirigia, 2009; Waitzman et al., 1994).

The resources are quantified using gross (top-down) costing and micro-costing (bottom-up) techniques with micro-costing adopting ingredient approaches including step-down full costing, activity-based costing, time and motion techniques, cross-sectional surveys, and manager interviews, whereas, gross-costing uses the historical outlay of resources to identify, measure and value costs of interventions (Mogyorosy & Smith, 2005). The prevailing market prices and opportunity costs (forgone benefits) are often adopted to value the resources for health services in monetary units (Conteh et al, 2004; Mogyorosy et al, 2005). Nonetheless, health market distortions attributed to monopolistic and oligopolistic pricing of the medical products have generated controversial debates on the accuracy of prevailing market prices as a measure of the forgone

benefits in economic evaluation studies (Conteh et al, 2004; Mogyorosy et al, 2005). The measure of productivity loss has similarly generated controversies due to the veracity of the estimated value of the forgone benefits attributed to illnesses (Conteh et al, 2004; Mogyorosy et al, 2005).

The value of the resources are subsequently categorized as recurrent (variable), and capital (fixed) costs and assigned to direct, indirect, and intermediate cost centres for allocation to the final cost center using ingredient techniques for computation of the total (final) costs of the services (Conteh & Walker, 2004; Cunningham, 2000; Drummond et al., 2015; Kirigia, 2009; McIntosh, 2006; Sandmann et al., 2018; Walker & Kumaranayake, 2002). Finally, statistical and sensitivity analyses should be conducted on the final costs to ascertain the robustness of the evaluation findings because of potential uncertainties arising from methods of determining the sample size and methods of collecting data for costing activities (Drummond et al., 2015). Capital costs are the value of resources that do not vary with the quantity of output in a short time, whereas recurrent costs are the value of resources often varying annually with the quantity of output (Drummond et al., 2015; Kirigia, 2009). Capital costs for more than one-year time horizon are discounted for differential timing using the current economic inflation rates or purchasing power parities to reflect the current net value of the resources (Conteh & Walker, 2004; Drummond et al., 2015; Kirigia, 2009; Walker & Kumaranayake, 2002). They include equipment, vehicles, and buildings, whereas recurrent costs comprise personnel emoluments, pharmaceuticals, non-pharmaceuticals, drugs, and staff-time (Drummond et al., 2015; Kirigia, 2009).

Direct, indirect, and intermediate cost centers sometimes share recurrent, and capital cost thus referred to as overheads (shared or joint) implying the value of resources used to provide more than one health intervention such as staff, buildings, and vehicles (Drummond et al., 2015; Kirigia, 2009). The overhead costs are proportionally allocated to the respective cost centres using economic techniques such as step-down cost accounting, the number of workers, and floor space, however, the use of these techniques has elicited controversial debates due to uncertainties arising from methods of gathering data for the costing activities (Conteh & Walker, 2004; Drummond et al., 2015; Kirigia, 2009; Mogyorosy & Smith, 2005; Walker & Kumaranayake, 2002).

Cost analysis studies were pioneered in the United States of America by Dorothy Rice in 1967 and have since been conducted widely in Europe and Australia, unlike developing countries attributed to the paucity of costing data, inaccurately profiled costing data, and inadequate costing expertise (Bhide et al., 2016; Bhide & Kar, 2018; Mugisha et al., 2002). Worldwide, the hospital charges for new-born children with some types of birth defects have been observed to range from four to eight times higher than those children without any form of birth defects (Simeone et al., 2015). In the United States, the expenditures on medical care for congenital anomalies were estimated at $ 1.4 billion per year and reported as the 5th leading cause of years of life lost to premature deaths in addition to infant morbidity and mortality in 1985 (Gilberto F. Chavez, 1988). The congenital anomalies were also noted to contribute significantly to chronic disease morbidity accounting for nearly 30% of all admissions to paediatric hospitals in the United States (Gilberto F. Chavez, 1988).

The human capital method was also used in 1992 to calculate direct and indirect costs of illnesses for the most clinically important structural birth defects in the United States (Lary & Edmonds, 1996, 1997). The study observed that the cost of specific birth defects ranged between $ 75,000 and $ 503,000; $ 503,000 for cerebral palsy, $ 451,000 for Down syndrome, and $ 294,000 for spina bifida (Lary & Edmonds, 1996, 1997). These defects recorded the highest total lifetime cost of $ 2.4 billion for cerebral palsy, $1.8 billion for Down syndrome, and $ 489 million for spina bifida; and a combined cost of $ 8 billion for 18 different types of structural birth defects in the United States (Lary & Edmonds, 1996, 1997). Additionally, direct costs of care of major birth defects were estimated at $ 2.6 billion in 2004 in the United States (Feldkamp et al., 2017; Mburia-Mwalili & Yang, 2014; Tinker et al., 2015). On the other hand, the costs of lifetime care of an infant born in a single year with at least one major birth defect were approximated at more than $ 6 billion in 2004 in the United States (Ouyang et al., 2007).

The economic burden of MESBDs can also be estimated in terms of Disability-Adjusted Life Years (DALYs) which is a metric measure of the disease burden described as a combination of the time lived with disability (YLD) and the time lost due to premature mortality (YLL) (Christianson et al., 2005, 2006; Wu et al., 2013). The years lost due to premature mortality (YLL) are estimated

using a standard life expectancy at each age, whereas, years lived with a disability are translated into an equivalent time loss using a set of weights reflecting the reduction in functional capacity (Christianson et al., 2005, 2006; Wu et al., 2013). The time spent in each state as YLD or YLL at different ages is adjusted using a set of "value choices" through age-weighting and discounting. Years lived with disability (YLD) are computed as a product of disease incidence (I) or prevalence (P), disability weights (DW), and length (L) of time to remission or death, thus, one DALY is equivalent to one healthy year (Preedy & Watson, 2010; Sitkin et al., 2015; Wu et al., 2013).

Worldwide, birth defects have also contributed substantially to the Global Burden of Disease (GDB) among children and are observed as the 17th leading cause of GBD (Sitkin et al., 2015; WHO, 2014, 2020; Wu et al., 2013). Additionally, the defects are also noted as the 10th leading cause of DALYs) accounting for 25 million DALYs and 2.9% of all YLD globally, largely borne by the developing countries (Hernandez-Diaz & Oberg, 2015; WHO, 2014; Wu et al., 2013). Defects of the central nervous system and orofacial clefts were noted to account for 21 million DALYs of which approximately 12 million were noted as preventable by surgical repairs thus underscoring the importance of accessible health services for these defects in developing countries (Sitkin et al, 2015). Notably, birth defects have been reported to cause disability in 150 million children and account for about 9% of the disease burden associated with conditions requiring surgical interventions globally (Sitkin et al., 2015; WHO, 2014, 2020; Wu et al., 2013).

In Gambia, birth defects accounted for the 2nd highest proportion of the surgical burden of disease followed by injuries, whereas 40% of surgical procedures performed at a leading hospital in Northern Nigeria were attributed to birth defects (Wu et al, 2013). Spina bifida had the greatest burden of the disease accounting for 54-120 DALYs per 1000 children, whereas the imperforate anus was associated with the highest Disability Weights (DW) at 0.85; followed by 0.6 for spina bifida, encephalocele, and bladder exstrophy each; 0.4 for hydrocephalus, 0.1 for hypospadias and clubfoot each; and 0.05 for cleft lip in Kenya (Wu et al., 2013). The costs of these defects have been noted to vary attributed to the extent of interventions related to the severity of the defects and long-term follow-up care such as spina bifida, encephalocele, hydrocephalus, and clubfoot (Wu et al., 2013).

2.11 Birth defect-related mortality

Worldwide, an estimated 134 million children are born every year of which approximately 7.9 million (6 -7%) are born with at least one severe birth defect, whereas about 3.3 million dies before the age of five, and 3.2 million of those surviving develop life-long physical disabilities (Bhandari, Sayami, K, & Banjara, 2015; Christianson et al., 2005, 2006; Lamichhane et al., 2016; WHO, 2014, 2020). Notably, more than 94% of such defects occur in developing countries where around 95% of the affected children do not survive beyond childhood partially attributed to MESBDs (Christianson et al., 2005, 2006). In every three infants who die one has at least a congenital anomaly, whereas 2 - 4% of the live births and 15 - 20% of the stillbirths have severe defects respectively globally (Anyanwu et al., 2015; Christianson et al., 2005, 2006; Sahib, 2016).

Congenital abnormalities remain one of the leading causes of infant mortality accounting for 20% in the United States, 2.25% in Europe, and 2.8% in Korea, however, its burden in South-East Asia regions is still not known (Lamichhane et al., 2016; Parker et al., 2010). The Lancet Child Mortality data estimated neonatal mortality rate due to congenital anomalies at 3 per 1000 births in 2010 in India (Khurmi et al., 2014). In Kenya, the neonatal mortality rate was estimated at 22 per 1000 live births with severe congenital anomalies accounting for approximately 13.8% between 2010 and 2015 (KDHS, 2015). The same study also estimated the infant mortality rate at 39 per 1000 live births and that of under-five at 52 per 1000 live births similarly attributed to MESBDs (KDHS, 2015).

2.12 Birth defect surveillance systems

The public health surveillance system is an ongoing systematic and continuous collection, management, analysis, interpretation, and dissemination of data on health events aimed at informing public health actions categorized as population and hospital-based methods (Rothman, Greenland, & Lash, 2008; Stehr-Green, Stehr-Green, Voetsch, & MacDonald, 2012; WHO, 2014, 2020). The criteria used to determine defects of high-priority for surveillance comprise; (i) frequency of the defects including incidence rates, prevalence rates, morbidity rates, and mortality rates, (ii) severity comprising case-fatality rates, hospitalization rates, and disability rates, (iii) preventability (modifiability), (iv) communicability (transmissibility/virulence), and (v) medical costs including direct and indirect costs (Lee, Thacker, & Louis, 2010; Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018; Rothman et al., 2008; Tinker et al., 2015).

The information gathered for hospital-based surveillance systems involves all cases of MESBDs that occurred in the selected hospitals for a given period within defined geographical regions or representative samples determined by probability sampling techniques from the cases observed in the same hospitals (Rothman et al., 2008; Stehr-Green et al., 2012; WHO, 2014, 2020). The denominator for estimating the prevalence of MESBDs from hospital-based data consists of the total number of births (live births and/or stillbirths) that occurred in the hospitals within the same study period (WHO, 2014, 2020). The numerator on the other hand comprises the total number of children who were born with MESBDs in the hospitals within the same study period (WHO, 2014, 2020). All children not born at the study hospitals are excluded in estimating the prevalence of the defects from hospital-based data despite being enumerated at the study facilities (WHO, 2014, 2020). The approaches to hospital-based surveillance systems include laboratory and sentinel-based methods aimed at providing a quick snapshot of adverse health outcomes to inform public health actions (Stehr-Green et al., 2012; WHO, 2014, 2020). Hospital-based surveillance systems are relatively cheap compared to population-based methods thus are preferred in resource-constrained countries (Khurmi et al., 2014; WHO, 2014, 2020).

The data collected for population-based surveillance systems on the other hand entail all cases of MESBDs that occurred among a defined population for a given period within a geographical region or a representative sample determined by probability sampling techniques from the cases observed in the region (Khurmi et al., 2014; WHO, 2014, 2020). The denominator for estimating the prevalence of MESBDs from population-based data consists of the total number of births (live births and/or stillbirths) that occurred in the region within the same study period (WHO, 2014, 2020). The numerator, on the other hand, comprises the total number of children who were born with MESBDs in the regions within the same study period (WHO, 2014, 2020). All the children born at health facilities and homes during the study period within the defined geographical region are included in estimating the prevalence of the defects (WHO, 2014, 2020). The prevalence of MESBDs estimated from population-based data is preferred in epidemiological studies because the results are generalizable to similar settings in the region unlike prevalence estimated from hospital-based data (Rothman et al., 2008; Stehr-Green et al., 2012). Community and school-based surveillance are examples of population-based surveillance systems where trained volunteers within the communities are used in community-based surveillance to detect and report cases of

MESBDs that might have not been reported to health facilities (Stehr-Green et al., 2012). Community-based surveillance systems identify people who are not seeking medical care, establish community health care networks, and strengthen relations between communities and healthcare systems within the locality (Stehr-Green et al., 2012). Community-based surveillance is more preferred in developing countries, however, it is likely to report a high rate of false-positive cases of the defects attributed to the inability of the community volunteers to correctly define the cases of MESBDs (Stehr-Green et al., 2012). School-based surveillance on the other hand screens all children enrolled in schools for MESBDs and referred to the health facilities for health care and gathering of the epidemiological data (Khurmi et al., 2014).

Case ascertainment strategies for collecting epidemiological data for surveillance systems include active, passive, or hybrid strategies (Stehr-Green et al., 2012; WHO, 2020). Vigorous ascertainment of cases by health agencies is referred to as active, whereas inactive ascertainment by health workers is known as passive, thus a combination of the two methods is described as enhanced-passive case ascertainment strategy of public health surveillance (Rothman et al., 2008; Stehr-Green et al., 2012; WHO, 2014, 2020). Although surveillance systems are known as integral epidemiological approaches to understanding the extent of public health problems, embedding variables for economic evaluation studies on surveillance systems for MESBDs would be of additional importance because the burden of these defects could be estimated both from public health and economic perspectives (Birch & Gafni, 1996; Briggs et al., 1994; Conteh & Walker, 2004; Lee et al., 2010; Modell et al., 2018; Waitzman et al., 1994; WHO, 2014, 2020). Different surveillance systems are developed within different political, social, geographic, economic, and historical contexts reflecting interests of individuals, training, and philosophies, however, no single model is universally applicable (Luquetti & Koifman, 2011). Nevertheless, robust public health surveillance systems would improve data quality and prevalence estimations to understand the public health magnitude of major external structural birth defects (Bhide et al., 2016).

Many developing countries are yet to establish birth defects surveillance systems contributing to underreporting of cases and grossly underestimated prevalence leading to the misconception of MESBDs as not of public health priority (WHO, 2014, 2020). Similarly, developing countries have

not recognized local epidemiological studies as a useful strategy for understanding the magnitude of MESBDs in the region also leading to the epidemiological fallacy (WHO, 2014, 2020). The highest burden of MESBDs is experienced in developing countries attributed to poverty and environmental pollution thus underscores the establishment of public health surveillance systems and registries as well as conducting epidemiological studies to define the baseline epidemiology of MESBDs in such settings (Mburia-Mwalili & Yang, 2014; Modell et al., 2018; Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018; Morris et al., 2018).

The World Health Organization has encouraged both developed and developing countries to conduct epidemiological studies, establish birth defect registries, and construct databases to understand the magnitude of the most common MESBDs in the region (WHO, 2014, 2020). Similarly, the World Health Organization has advised countries without public health surveillance systems to adopt at least a hospital-based surveillance system to lay foundations for population-based surveillance systems providing snapshots of the problem allowing for generalization of the results to similar settings within the region (Khurmi et al., 2014; WHO, 2014, 2020). The World Health Organization also proposed a three-staged public health surveillance strategy for major external structural birth defects consisting of; (i) the interventions aimed at preventing nearly 50% of birth defects whose causes are modifiable, (ii) improvement of locally available care, and (iii) treatment of infants with genetic diseases known to be curable (Luquetti & Koifman, 2011).

The importance of epidemiological data on birth defects was first recognized in the reverberation of the six-years Second World War that occurred between September 1st, 1939, and September 2nd, 1945 (Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018). This led to the establishment of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) to collate and correlate information on the levels of exposures and evaluate the effects of populations' exposure to ionizing radiation (Moorthie, Blencowe, Darlison, Lawn, Mastroiacovo, et al., 2018). UNSCEAR meticulously conducted controlled prevalence studies on birth defects in Hiroshima and Nagasaki populations on the assumption that exposure to ionizing radiation would lead to increased mutation rates and manifest as increased prevalence of birth defects in children globally (Modell et al., 2018; Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018). The studies by

UNSCEAR provided the foundation for the progressive formation of the national birth registries beginning with the British Columbia Health Surveillance Registry (BCHSR) in 1952, and National Hungarian Congenital Abnormality Registry (NHCAR) in 1962 (Modell et al., 2018).

The famous thalidomide tragedy of the 1960s also triggered and strengthened the need for birth defect registries and surveillance systems across the world (Mburia-Mwalili & Yang, 2014; Modell et al., 2018; Morris et al., 2018). The thalidomide disaster was established in 1964 when an increased number of children born with limb deformities was observed in Germany and other jurisdictions where it was used for the treatment of hyperemesis gravidarum (Mburia-Mwalili & Yang, 2014; Modell et al., 2018; Morris et al., 2018). Further, the discovery of maternal rubella infection (German measles) in 1942 which is a powerful teratogen with adverse health effects, laboratory identification of the virus in 1962, the 1964 global epidemic that affected about 1% of the pregnancies, and increased technical diagnostic capacity of the virus also boosted the recognition of congenital disorders as a global public health problem (Mburia-Mwalili & Yang, 2014; Modell et al., 2018; Morris et al., 2018). Similar observations have been made recently including the associations of microcephaly with zika virus in South America, and dolutegravir which is antiretroviral medicine with neural tube defects in South Africa (Mburia-Mwalili & Yang, 2014; Modell et al., 2018; Morris et al., 2018).

Surveillance programs are of public health significance because they could demonstrate distribution, trends, and patterns of the defects as well as elucidate risks factors, evaluate prevention and assess treatment strategies for the defects (Conteh & Walker, 2004; Cunningham, 2000; Lee et al., 2010; Luquetti & Koifman, 2011; Morris et al., 2018; Stehr-Green et al., 2012; WHO, 2014, 2020). Consequently, surveillance systems could be used to determine the epidemiology of MESBDs to inform planning and allocation of resources for the health services in the region (Bhide et al., 2016; Bhide & Kar, 2018; Khurmi et al., 2014; Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018; Moorthie, Blencowe, Darlison, Lawn, Mastroiacovo, et al., 2018).

2.13 Birth defect registries

Birth defect registries have progressively been established beginning with the British Columbia Health Surveillance Registry (BCHSR) in 1952 informed by the controlled studies by UNSCEAR; and NHCAR in 1962 which partnered with the Hungarian Optional Programme which is a public health initiative (Modell et al., 2018). These registries pioneered the collection of invaluable epidemiological data for estimating the magnitude of severe structural birth defects and conducting randomized controlled trial interventions for the defects with a view of assessing the effectiveness of preconception folic acid/multivitamins supplementation to improve birth outcomes (Modell et al., 2018). The two main surveillance advantages that countries with birth defect registries have over those without are; (i) they can define baseline epidemiology of important congenital anomalies to facilitate programs, policy, and resource planning; and (ii) they can identify groups of cases and other epidemiological changes that give early warnings of environmental hazards (Moorthie, Blencowe, Darlison, Lawn, Mastroiacovo, et al., 2018).

Even though setting up sustainable surveillance systems and registries for birth defects is resource-intensive for the countries that are yet to establish such programs, they are still required to generate prevalence estimates of the most common congenital anomalies as the starting point for assessing the burden of disease and implications of the health services (Moorthie, Blencowe, Darlison, Lawn, Mastroiacovo, et al., 2018). The registries which have since been established include European Surveillance of Congenital Anomalies and Twins (EUROCAT), International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), National Birth Defects Prevention Network (NBDPN), Latin American Collaborative Study of Congenital Malformations (ECLAMC), and the South-East Asia Region's New-born and Birth Defects Database (SEAR-NBBD) (Blencowe, Kancherla, Moorthie, Darlison, & Modell, 2018; Blencowe, Moorthie, Darlison, Gibbons, & Modell, 2018).

2.14 Birth defect surveillance in Kenya

Kenya is among the many developing countries that have not established national public health registries and surveillance systems yet epidemiological and cost analysis studies based on hospital-based data to estimate the burden of MESBDs are rare in the region (Bhide et al., 2016; Bhide & Kar, 2018; Githuku et al., 2014; Muga et al., 2009; Wu et al., 2013). Detection of the congenital

anomalies is carried out by primary health care providers in maternity units through initial and routine physical examination of the newborn children soon after birth for recording in maternity files and registers for compilation of the monthly reports along with other birth outcomes. The health care providers responsible for childbirths in the maternity units have no specialized training on the detection of birth defects compounding inaccurate medical records and unreliable health statistics for MESBDs in the region. The detection of the defects entirely depends on the personal knowledge, attitude, and skills of the health professionals including the midwives, medical officers, obstetricians, and paediatricians in the hospitals leading to under-reporting of birth defects in the country.

The information is continuously gathered as standard operating procedures in maternity units, summarised on monthly basis as congenital anomalies, and entered in District Health Information System (DHIS) to provide a general overall snapshot of the public health magnitude of the defects nationally regardless of the specifications of their severity, and types. Nonetheless, the Ministry of Health in partnership with the Center for Disease Control has since established a pilot study for the easily recognizable birth defects including neural tube defects, orofacial clefts, and congenital talipes equinovarus in selected hospitals which began in 2016 at Pumwani maternity hospital in Nairobi county followed by other hospitals consisting of Nyamira county referral hospital, Kilifi county referral hospital, and Naivasha sub-county hospital among other hospitals in the region.

2.15 Birth defect registry in the United States

The objective of initiating a birth defect surveillance system in the United States was intended to promote quality data including comparability, completeness, and timeliness to enhance research on the distribution, etiology of birth defects, to promote the use of surveillance data for evaluation and link affected children with services (Sever, 2004). Before 1999, the national prevalence for birth defects was estimated from hospital-based surveillance data drawn from the Birth Defects Monitoring Program (BDMP) which used hospital discharge data to ascertain the number of congenital anomalies diagnosed at birth in the United States (Canfield et al., 2006; WHO, 2014, 2020).

The program estimated the prevalence of congenital anomalies at 3%, however, it was thought to have been underestimated thus necessitating the need for accurate prevalence estimation using population-based data in the United States (Canfield et al., 2006; WHO, 2014, 2020). This observation consequently informed the establishment of the National Birth Defects Prevention Network (NBDPN) to gather data for congenital anomalies using population-based surveillance systems in 34 states in the United States of America (Canfield et al., 2006; WHO, 2014, 2020). NBDPN was tasked to describe and estimate the annual national prevalence of specific birth defects to provide a snapshot of the public health magnitude of the defects in the United States from 1999–2001 (Canfield et al., 2006; Parker et al., 2010; WHO, 2014, 2020), and to participate also in collaborative birth defect researches in the region (Parker et al., 2010). NBDPN approximated the national prevalence of 21 birth defects from 1999 to 2001 which observed anencephaly, Anophthalmia/microphthalmia, cleft lip with/without palate, and reduction of upper limbs as the most prevalent defects in the United States (Parker et al., 2010).

2.16 Birth defects registry in Brazil

Birth defects were reported as the second leading cause of infant mortality (16.3%) in 2005, thus in Brazil, birth certificates were revised in 2000 to include a field for recording types of birth defects in its hospital-based surveillance system to link birth defects epidemiological data to the national civil registration database (Luquetti et al, 2011).

2.17 Birth defect registry in Europe

European Surveillance of Congenital Anomalies and Twins (EUROCAT) and International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) were established as umbrella registries in 1974 in Europe (Modell et al., 2018). The registries were intended to collect, standardize, and harmonize prevalence for birth defects from the individual registries and publish key reference data in Europe regularly (Modell et al., 2018). The birth outcomes reported by the registries included live-births, terminated pregnancies for foetal impairment, foetal deaths, and stillbirths thus informing estimation of prevalence and the effects of public health interventions for specific birth defects in the region (Modell et al., 2018). The registries were also initiated to monitor the existing trends, discover new trends, identify risk factors, and evaluate the effectiveness of primary prevention policies for specific birth defects in Europe (Cavadino et al., 2016).

The EUROCAT is a network of population-based congenital anomaly registries in Europe which aimed at gathering information on severe birth defects, live-births, foetal deaths of at least 20 weeks gestation, and electively terminated pregnancies for foetal anomalies in the region (Boyle et al., 2018). The registry collected data on 1.7 million births from 43 registries in 23 countries in Europe from 2003 to 2012 (Cavadino et al., 2016), and estimated the overall prevalence of birth defects at 248.6 per 10000 live births from 2010 to 2014 in Europe (Pasha et al., 2017). ICBDSR on the other hand collected additional data from low-middle and high-income counties across the world and observed that approximately 30% of birth defects could be reliably diagnosed around the time of birth in the absence of advanced facilities (Modell et al., 2018).

2.18 Birth defect registry in Asia

In China, a facility-based surveillance system was initiated in 1986 with a paper-based data reporting method which was replaced by an electronic-web-based reporting system developed by the National Office for Maternal and Child Health Surveillance in 1998 (Chen et al., 2018). The surveillance program initially used facility-based data to monitor 23 types of birth defects based on ICD-10 classification (Chen et al., 2018). In Iran, The Tabriz Registry of Congenital Anomalies (TRoCA) was set up in 2000 by ICBDSR and EUROCAT supported by local and national funds as a pilot model for setting up a nationwide registry of congenital anomalies in the region (Stone et al., 2017). TRoCA intended to register the occurrence of selected defects; prepare epidemiological indexes to indicate magnitude and trends of the problem over time; monitor emerging and most prevalent birth defects; avail valid data on birth defects to policymakers; plan and implement preventive and control strategies for selected birth defects; and to evaluate prevention and control strategies for the defects in the region (Stone et al., 2017). The registry produced invaluable epidemiological data for etiological investigations, methodological studies, service provision, and preventive measures for selected congenital anomalies thus achieving its intended goals in the region (Stone et al., 2017).

India is among many that do not have an established national surveillance system for congenital anomalies, however, the data for prevalence estimation is drawn from hospital-based cross-sectional studies (Bhide et al., 2016; Bhide & Kar, 2018). In India, prevention for birth defects received attention for the first time when screening for congenital anomalies was launched as a

new intervention and incorporated in national child health services from February 6th, 2013 (Khurmi et al., 2014). The initiated child health services were envisaged to screen, treat and manage a set of health conditions such as birth defects, nutritional deficiencies, disease, disabilities and delayed developmental milestones in India (Khurmi et al., 2014). All children born at public health facilities, born at home and those enrolled in public schools would be screened for the anomalies and referred to appropriate facilities for further management by health workers (Khurmi et al., 2014). The introduction of screening of new-born infants for birth defects facilitates early detection, effective life-saving medical treatment, surgery, rehabilitation, and rehabilitative care for the affected children (WHO, 2010).

2.19 Conclusions

Worldwide, major external structural birth defects are a public health problem associated with prenatal deaths, childhood morbidity, childhood mortality, and children who survive to adulthood suffer lifelong resource-intensive physical disabilities. Lifesaving medical and surgical interventions are of great public health importance in improving child survival and dealing with the adverse health effects, whereas public health surveillance systems, epidemiological studies, and economic evaluation of the defects help in understanding the burden associated with these defects regionally.

CHAPTER THREE: PREVALENCE OF MAJOR EXTERNAL STRUCTURAL BIRTH DEFECTS IN KIAMBU COUNTY, KENYA: 2014-2018

Abstract

Introduction: Major external structural birth defects are typical and have been associated with childhood morbidity, mortality, and lifelong resource-intensive disabilities. These defects continue to occur; however, they are yet to be recognized as public health problems in Kenya.

Objective: The objective of this study was to estimate the prevalence of major external structural birth defects in Kiambu County in Kenya from 2014 to 2018.

Methods: A hospital-based descriptive cross-sectional study design was adopted in this study where a retrospective review of medical records for five years between 2014 and 2018 was conducted from April 1st, 2019, to July 12th, 2019. The study enumerated all the cases of birth defects (873) recorded in the medical records in the five years; however, a five-year prevalence numerator of 362 cases was considered following a predetermined inclusion criterion, whereas a five-year prevalence denominator of 299,854 cases of registered live births was obtained from the Birth Registrar. Data drawn from secondary data abstraction tools were double-entered into an excel-spreadsheet by two independent data clerks to minimize errors. The Principal Investigator (PI) exported the validated dataset to Stata software, version 14 (Stata Corporation, College Station, Texas, USA) for cleaning and analyses. Descriptive categorical variables were summarized in frequency tables, proportions, and percentages to show their distributions. Annual prevalence estimates of 29 sub-groups and 6 groups of these defects were calculated as the number of cases (numerator) divided by the number of live births (denominator). Associated 95% binomial exact confidence intervals were also computed and expressed per 100000 live births.

Results: There was an annual increasing prevalence trend of six groups of major external structural birth defects affecting the musculoskeletal, central nervous system, orofacial, genital, eye, and anus organ systems ranging from 44.04 (95% CI: 27.92-66.07) and 205.28 (95% CI: 173.15-241.64) per 100000 live births between 2014 and 2018. Defects of the musculoskeletal system were the most prevalent ranging from 22.98 [95% CI: 11.87-40.13] to 116.9 [95% CI: 92.98-145.08] per 100000 live births followed by neural tube defects from 13.40 [95% CI: 5.39-27.61] to 32.79 [95% CI: 20.79-49.19] per 100000 live births between 2014 and 2018.

Conclusions: The study showed an increasing prevalence trend of the defects in the county; thus, I would recommend an epidemiological study to identify the potential risk factors for the defects.

Keywords: Major external structural birth, defects, prevalence, county, Kenya

3.1 Introduction

Worldwide, an estimated 134 million births are reported to occur each year of which 7.9 million (6%) are born with at least a major birth defect, mostly affecting the musculoskeletal system and the central system (Christianson et al., 2005, 2006; WHO, 2013, 2014, 2020). Birth defects are defined as abnormalities of intrauterine origin that affect the development of body structures or functions and are present from birth (Christianson et al., 2005, 2006; WHO, 2013, 2014, 2020). Approximately 30% of these defects are clinically obvious and can be reliably diagnosed either at birth or soon after in the absence of advanced medical techniques (Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018; Moorthie, Blencowe, Darlison, Lawn, Mastroiacovo, et al., 2018; Parker et al., 2010; Tinker et al., 2015; WHO, 2014, 2020). Birth defects may be classified according to health-related impacts and described as major or minor defects (WHO, 2014, 2020). Alternatively, they may be classified based on anatomical locations and referred to as external or internal defects (WHO, 2014, 2020). Thus, major external structural birth defects (MESBDs) are physical abnormalities detectable at birth that have significant health and developmental impacts on the affected children (Christianson et al., 2005, 2006; WHO, 2013, 2014, 2020).

These defects continue to occur and exert an enormous financial burden to the affected individuals, health services, and societal welfare, however, they have been neglected, underestimated, and unappreciated as public health problems (Andegiorgish et al., 2020; Christianson et al., 2005, 2006; Feldkamp et al., 2017; Sitkin et al., 2015; Tinker et al., 2015). Globally, birth defects are among the leading causes of disability-adjusted life years (DALYs), accounting for 25 million DALYs, and 2.9% of years of life lived with disabilities (Bhide et al., 2016; Bhide & Kar, 2018; Christianson et al., 2005, 2006; WHO, 2014, 2020; Wu et al., 2013). Although birth defects are widespread across the world, the highest-burden occurs in middle-and low-income countries (Christianson et al., 2005, 2006; WHO, 2014, 2020; Wu et al., 2013). Worldwide, the prevalence of major external birth defects has been noted to vary by types, severity, and geographical regions attributed to data paucity and case under-reporting (Bhide et al., 2016; Bhide & Kar, 2018; Feldkamp et al., 2017; Khurmi et al., 2014; Tinker et al., 2015; Wellesley et al., 2005; Wellesley et al., 2004).

In middle-income countries, the prevalence of these defects was estimated at 5.6%, whereas, in low-income countries it was estimated at 6.4%, largely affecting musculoskeletal and central nervous systems (Christianson et al., 2005, 2006; Feldkamp et al., 2017; Sitkin et al., 2015; Tinker et al., 2015). Similarly, defects of the musculoskeletal and central nervous systems were observed to occur more frequently than other MESBDs in Kenya, accounting for 33.9%, and 28.6%, respectively (Githuku et al., 2014; Muga et al., 2009). In 2010, the prevalence of MESBDs was estimated at 6.3 per 1000 live-births with congenital talipes equinovarus (CTEV), a musculoskeletal disorder being the most common (2.9 per 1000 live-births) in Kenya (Wu et al., 2013). Neural tube defects (NTD) followed closely at 0.9 per 1000 live-births for hydrocephalus, 0.5 per 1000 live-births for spina bifida, and 0.4 per 1000 live-births for encephalocele (Wu et al., 2013). Additionally, hypospadias, a defect of the male genital organ was estimated at 0.9 per 1000 live-births, whereas, cleft lip and imperforate anus were estimated at 0.4 and 0.2 per 1000 live-births, respectively (Wu et al., 2013). Notably, spina bifida was reported to have the highest burden of the disease in Kenya, despite a relatively low prevalence estimate (Wu et al., 2013).

Intrauterine foetal development (embryogenesis) occurs in the first 8 weeks of gestation (first-trimester of gestation); a period of great public health importance because of its vulnerability to teratogenicity and the effectiveness of preventive strategies (Taye et al., 2016; Tinker et al., 2015). Similarly, twelve weeks to conception are significant due to the susceptibility of women of reproductive age to teratogens and the appropriateness of effective public health preventive interventions (Taye et al., 2016; Tinker et al., 2015). Thus, twelve weeks before conception and eight weeks after conception are critical for effective prevention and control of major external structural birth defects (Christianson et al., 2005, 2006; Finer & Zolna, 2014, 2016; Tinker et al., 2015). However, approximately half of pregnancies are usually unplanned, coupled with difficulties in identifying these women during this period and the inability to recognize many pregnancies until the end of the first trimester when the defects have already formed (Christianson et al., 2005, 2006; Finer & Zolna, 2014, 2016; Tinker et al., 2015). Despite these observations, little investments have been directed to public health research, prevention, and control activities for these defects in Kenya. Therefore, the objective of this study was to estimate the prevalence of major external structural birth defects in Kiambu County, Kenya.

3.2 Methods

3.2.1 Study settings and design

This study was conducted in 13 public hospitals within Kiambu County in Kenya, whose health department comprised of community health services, 70 dispensaries, 24 health centres, 10 sub-county hospitals, and 3 county referral hospitals. The 13 study hospitals consisted of the ten sub-county hospitals; Kihara, Karuri, Wangige, Nyathuna, Lari-Rukuma, Ruiru, Tigoni, Lussigetti, Kigumo, and Igegania, and the three county referral hospitals; Kiambu, Thika, and Gatundu. These hospitals were purposively selected for offering reproductive, medical, paediatrics, and surgical health services in the 13 sub-counties of Kiambu County. Community health services, dispensaries, and health centres collaboratively link women for reproductive health services and children born with major external structural birth defects to the study hospitals for medical and surgical care. It is the second-most densely inhabited of the 47 counties with approximately 2.4 million of the 47.5 million nationally underpinning sample representativeness of the study population (KNBS, 2019). Nairobi City County is the highest populated with an estimated population of 4.3 million, whereas Nakuru County is the third-most populated estimated at 2.1 million (KNBS, 2019). Kiambu County is largely urbanized a regional commercial hub, and the wealthiest bordering Nairobi City County to the South, Muranga, and Nyandarua Counties to the North, Nakuru, and Kajiado Counties to the West (KNBS, 2019). All most of all births (96.5%) take place in health facilities, whereas about 96.9% of the births are notified for registration for the subsequent issuance of birth certificates in the county (KNBS, 2019). Thus, merely about 3% of the births in the county occurred during the study period similarly underpinning the representativeness of the prevalence denominator. Additionally, about 2.2% of its inhabitants aged five years and above are living with lifelong disabilities attributed to congenital anomalies pointing to the prevalence of and risk factors for MESBDs in the county (KNBS, 2019; Mugoya & Mutua, 2015). Agriculture (coffee, tea, and dairy farming) is the economic mainstay of the county as well as being one of the leading innovative commercial hubs locally. The study adopted a hospital-based descriptive cross-sectional design to estimate the prevalence of major external structural birth defects; being the best choice of study design for measuring population attributes, providing snapshots of salient public health problems, and allowing for results generalization in similar settings. This was an observational study, hence was reported as per the STROBE (strengthening

the reporting of observational studies in epidemiology) guidelines (Cuschieri, 2019; Da Costa, Cevallos, Altman, Rutjes, & Egger, 2011).

3.2.2 Study population and eligibility for participation

The study population (prevalence denominators) comprised all children born to resident women of Kiambu County between January 1st, 2014, and December 31st, 2018. Cases (prevalence numerators) were defined as live births with at least one clinically obvious major external structural birth defect referenced and/or described by a primary healthcare provider, either in the delivery rooms or neonatal units. These defects were considered for this study because they were easily recognizable visually or through physical examination at birth or shortly after birth by a healthcare provider. Additionally, case ascertainment was less likely to be affected by regional differences in referral and medical treatment compared to other anomalies. Primary health care providers consisted of midwives, medical officers, and obstetricians in delivery rooms, whereas, in neonatal units, the primary providers comprised the nurses, midwives, medical officers, clinicians, and paediatricians. The choice of the study population helped to provide a glimpse of the public health magnitude of these defects in Kiambu Country. Thus, the study results acted as a pointer to the "silent epidemic", and were intended to inform public health planning, policy decisions, and actions on public health surveillance and birth defect-specific interventions, such as defect-specific surveillance systems, risk assessments, and preventive strategies.

3.2.3 Exclusion criteria

The study excluded stillbirths, new-borns to non-resident women of Kiambu County, and new-borns with clinically undetectable or unobvious birth defects at birth or soon after birth. Additionally, externally occurring structural birth defects with no significant medical and financial implications were also excluded from the study.

3.2.4 Sources and collation of numerator and denominator data

The study extracted numerator data from the medical records consisting of maternity files, maternity registers, neonatal inpatient files, and neonatal daily bed returns. Maternity files contain records about women admitted to the delivery rooms for childbirth. Information captured in these files includes demographic, social, medical, surgical, and reproductive history, admission findings, intrapartum, and postpartum care. These files have summary sections for recording birth defects visually identified at birth or soon after birth by the primary health care providers. Summaries of

the maternity files are then entered into maternity registers for the compilation of hospital reports thus used as complementary sources of data in this study. Similarly, neonatal inpatient files contain maternal information described in the maternity files above, and information of the neonates. The information about neonates is further summarized in daily bed returns thus used as supplementary sources of data in this study.

Before data collection, six research assistants (four nursing graduate interns, and two health records/information graduate interns) were recruited and trained in data extraction techniques to ensure that the abstraction process was carried out in a standardized manner. To obtain the numerator data, medical-related records described above were reviewed over the five-year study period. All cases of MESBDs referenced and/or described by primary health care providers were extracted from the medical records described above between April 1st, 2019, and July 12th, 2019, and entered in a predefined data abstraction tool by the data extractors and the Principal Investigator. Information captured during data extraction included names of the study hospitals, sources of data, sub-county of residence, dates of admission, dates of birth, sex of the new-born children, definitions or descriptions of the birth defects, referrals from homes, peripheral health facilities, and to other health facilities.

On the other hand, annual prevalence denominators (the number of registered live births) between 2014 and 2017 were drawn from the Kenya Vital Statistics Report, 2017 (KVSR 2017); a publication of Civil Registration Services (CRS, 2018), whereas the denominator was provided as supplementary information awaiting publication. The registration process begins with the notification of births by health workers and assistant chiefs as civil registration assistants who enter the information of the new-born children in birth notification registers. The birth notification register is filled in duplicate known as Acknowledgement of Birth Notification; the counterfoil copies are retained by registration assistants, whereas the original slips are given to the parents or next of kin for the subsequent issuance of official birth certificates. These registers contain variables such as sex (male/female), type of birth (single/multiple), and nature of birth (alive/dead). The sampling flow chart for the collation of the numerator data for the prevalence study is illustrated below **(Figure 1).**

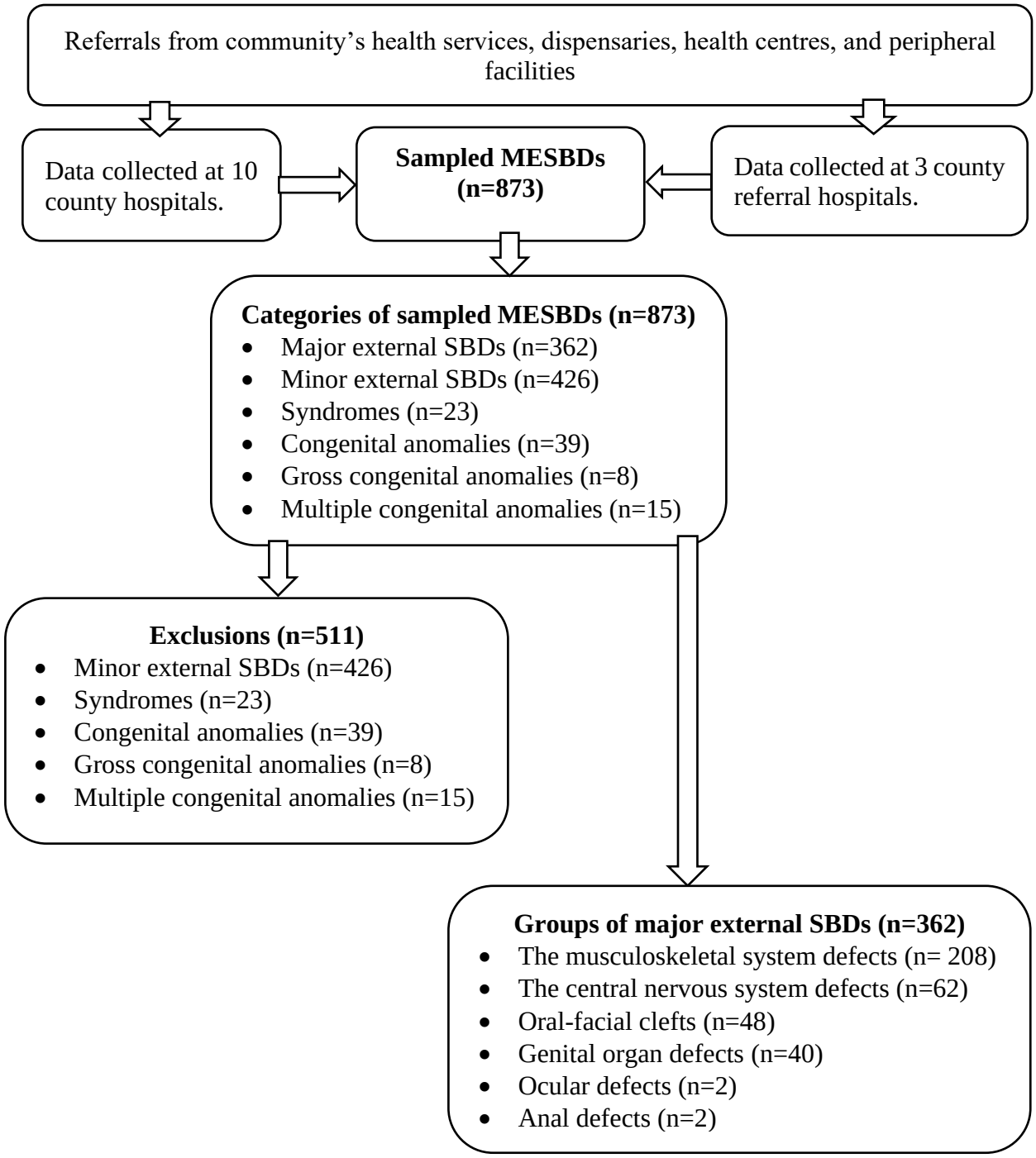


Figure 1: Flow chart for the numerator sampling strategy

3.2.5 Ethical approvals, authorizations, and considerations

Ethical approval was obtained from Kenyatta National Hospital (KNH)-University of Nairobi (UoN) Ethics Review Committee (Ref. No: KNH-ERC/A/44). The National Commission for Science, Technology, and Innovation further granted us permission vide a letter Ref. No:

NACOSTI/P/19/75586/28325 to collect data in Kiambu County. The County Commissioner of Kiambu also provided an authorization Ref. No: ED.12 (A)/1/VOL.11/107 and copied to the County Director of Education who acknowledged by stamping the letter. The County Director of Health, Kiambu County similarly authorized this study to vide a letter Ref. No: KIAMBU/HRDU/AUTHO/2019/03/06/AgotGN. The study was conducted in 13 county hospitals (3 county referral, and 10 sub-county hospitals) which granted additional permissions through written authorizations or counter approving the authorization letter issued by the County Health Directorate. The Medical Superintend of Thika county referral hospital authorized the study to vide a letter Ref. No. MOMS/TKA/VOL.III (728), whereas Gatundu county referral hospital issued an authority vide a letter Ref: GTD/GEN/37/VOL.1/97. The Director of Civil Services (Kenya) further provided the denominator data vide an authorization letter Ref: CR/ADM/149/049/TY/47. The data collected were de-identified using anonymous codes and entered in a laptop secured by an alphanumeric coded key only known to the PI to maintain confidentiality.

3.2.6 Minimization of biases

The study anticipated selection, referral, information, and ascertainment biases; therefore, deliberate attempts were made to reduce their occurrence in this study. First and foremost, the Principal Investigator predefined an eligibility criterion (case definitions) for participation in the study to reduce selection and referral biases; the residence for inclusion in this study was also well specified for this purpose. Similarly, the PI predetermined a secondary data abstraction tool to reduce cases of information biases in the study. All cases of external structural birth defects recorded in the medical records for the five-year study period (2014-2018) were listed in the data abstraction tools also to help in reducing cases of ascertainment, and information biases in this study. Further, the numerator (cases) considered for estimating the prevalence of MESBDs was solely determined by the PI regarding the definition of cases also to reduce the likelihood of experiencing case ascertainment, and information biases in this study.

Secondly, data collectors were trained on retrieval of the medical records from medical records stores/shelves, secondary data extraction techniques from the medical records, data entry into the abstraction tools, and subsequent re-shelving of the medical records to standardize the information gathered thus reducing information biases in this study. Health records/information graduate

interns (RAs) were specifically assigned the duties of pulling and re-shelving (retrieval) of the medical records to reduce double entry of data, whereas the nursing graduate interns were assigned data extraction from the medical records to ensure that the process was carried out in a standardized manner, thus reduced information, and selection biases, respectively. The allocation of these duties to the RAs was informed by professional expertise; health information interns were the subject matter experts in records retrieval whereas the nursing interns were the subject matter experts in clinical information. Information bias was reduced further by using maternity registers as complementary data sources to maternity files where the files were inaccessible, whereas neonatal daily bed returns were complementary to inaccessible neonatal files. The medical records (maternity files, neonatal files, maternity registers, neonatal unit registers, and neonatal daily bed returns which were in circulation during data collection were traced to the service points where the data were extracted, and files left secured in the respective stations, thus further reduced the likelihood of information biases.

3.2.7 Statistical analysis

Data obtained from secondary data abstraction tools were double-entered into an excel-spreadsheet by two independent data clerks to minimize errors. The Principal Investigator (PI) exported the validated dataset to Stata software, version 14 (Stata Corporation, College Station, Texas, USA) for cleaning and analyses. Descriptive categorical variables were summarized in frequency tables, proportions, and percentages to show their distributions. The prevalence estimates of major external structural birth defects were calculated as the number of cases (numerators) divided by the total number of live births (denominators) using the formula below: -

$$\boldsymbol{Prevalence} = \frac{\boldsymbol{Numerator}}{\boldsymbol{Denominator}} \times \boldsymbol{100,000\ live\ births} \qquad \boldsymbol{Equation\ (1)}$$

Associated 95% binomial exact confidence intervals were also computed and expressed per 100000 live births. Summary results were presented in proportions using frequency tables and graphs to show the distribution of major external structural birth defects in the county.

3.3 Results

The results for the prevalence study were reported as frequency distributions, prevalence estimates, and prevalence trends of major external structural birth defects for five years from 2014-2018.

3.3.1 Frequency distribution of major external structural birth defects, 2014-2018

The study observed 362 cases categorized into six groups and 29 specific types of major external structural birth defects **(Table 1).** Defects of the musculoskeletal system (57.46%) were the most frequent of the six groups of major external structural birth defects followed by defects of the central nervous system (17.13%), orofacial defects (13.26%), and defects of the genital organs (11.05%) **(Table 1).** Anal (0.55%), and ocular (0.55%) defects were also observed in the county during the study period **(Table 1)**. Of the 29 (362 cases) specific types of MESBDs, congenital tailpipes equinovarus (42.0%), was the most common followed distantly by cleft lip with the palate (10.22%), and hypospadias (9.11%), respectively **(Table 1).** Reduction defects of the limbs (5.52%), anencephaly (5.25%), and hydrocephalus (4.42%), and spina bifida (2.76%) were similarly common **(Table 1).** Notably, congenital talipes equinovarus (42%) was observed as the most prevalent MESBDs among the 29 specific groups of MESBDs followed by cleft lip with the palate (10.22%) and hypospadias 9.11%) **(Table 1).**

Table 1: Proportions of groups and specific types of MESBDs among children in Kiambu County, 2014-2018 (N=362)

Groups of MESBDs	Specific types of MESBDs (N=362)	Frequency	Percent
Musculoskeletal system defects	**Sub-total (n)**	**208**	**57.46**
	Congenital talipes equinovarus	152	42.00
	Reduction defects of the limbs	20	5.52
	Clubbed hand	7	1.93
	Ectrodactyly	1	0.28
	Congenital knee defects	7	1.93
	Conjoint twins	1	0.28
	Gastroschisis	12	3.32
	Omphalocele	8	2.21
Central nervous system defects	**Sub-total (n)**	**62**	**17.13**
	Anencephaly	19	5.25
	Hydrocephalus	16	4.42
	Spina bifida	10	2.76
	Microcephaly	4	1.10
	Craniorachischisis	2	0.55
	Encephalocele	2	0.55
	Meningocele	2	0.55
	Neurological defect	1	0.28
	Sacrococcygeal teratoma	1	0.28
	Craniosynostosis	1	0.28
	Congenital scoliosis	4	1.10

Oral-facial clefts	**Sub-total (n)**	**48**	**13.26**
	Cleft lip with palate	37	10.22
	Cleft lip without palate	7	1.93
	Cleft palate	4	1.10
Defects of genital organs	**Sub-total (n)**	**40**	**11.05**
	Hypospadias	33	9.11
	Epispadias	4	1.10
	Unformed genitalia	1	0.28
	Malformed penis	2	0.55
Defects of eye	**Sub-total (n)**	**2**	**0.55**
	Anophthalmia	1	0.28
	Congenital cataract	1	0.28
Defects of anus	**Sub-total (n)**	**2**	**0.55**
	Imperforate anus	2	0.55
All MESBDs	**Total**	**362**	**100.00**

MESBDs, Major External Structural Birth Defects

Congenital talipes equinovarus (73.08%) was similarly noted as the most prevalent defect among MESBDs of the musculoskeletal system during the study period, followed by limb reduction defects and abdominal wall defects estimated at 9.62% each **(Table 2).** Notably, limb reduction defects (9.62%) consisted of unspecified lower limb reduction (5.77%), unspecified upper limb reduction defects (1.92%), Phocomelia (0.96%), Amelia (0.48%), and congenital femoral deficiency (0.48%), whereas abdominal wall defects comprised gastroschisis (5.77%), and omphalocele (3.85%) (**Table 2).** On the other hand, congenital knee defects consisted of Arthro-onchyo-dysplasia (0.96%), congenital patella aplasia (0.48%), and congenital patella dysplasia (1.92%) accounting for 3.36% of the MESBDs of the musculoskeletal system **(Table 2).** The study further showed anencephaly (30.65%), hydrocephalus (25.81%), and spina bifida (16.13%) as the common among the defects of the central nervous system **(Table 2).** Of the defects of orofacial structures, cleft lip with the palate, cleft lip without palate, and cleft palate accounted for 77.08%, 14.58%, and 8.33%, respectively **(Table 2).** Conspicuously, hypospadias, a defect of the male genital organ accounted for 82.5%, whereas epispadias accounted for 10% of defects of the genital organs observed during this study **(Table 2).**

Table 2: Proportions of specific types of MESBDs among children in Kiambu County, 2014-2018

Groups of MESBDs	Specific types of MESBDs	Frequency	Percent
Musculoskeletal system defects	**Sub-total (N)**	**208**	**100.00**
	Congenital talipes equinovarus	152	73.08
	Reduction defects of the limbs	20	9.62
	Clubbed hand	7	3.37
	Ectrodactyly	1	0.48
	Congenital knee defects	7	3.37
	Conjoint twins	1	0.48
	Gastroschisis	12	5.77
	Omphalocele	8	3.85
Central nervous system defects	**Sub-total (N)**	**62**	**100.00**
	Anencephaly	19	30.65
	Hydrocephalus	16	25.81
	Spina bifida	10	16.13
	Microcephaly	4	6.45
	Craniorachischisis	2	3.23
	Encephalocele	2	3.23
	Meningocele	2	3.23
	Neurological defect	1	1.61
	Sacrococcygeal teratoma	1	1.61
	Craniosynostosis	1	1.61
	Congenital scoliosis	4	6.45
Oral-facial clefts	**Sub-total (N)**	**48**	**100.00**
	Cleft lip with palate	37	77.08
	Cleft lip without palate	7	14.58
	Cleft palate	4	8.33
Defects of genital organs	**Sub-total (N)**	**40**	**100.00**
	Hypospadias	33	82.50
	Epispadias	4	10.00
	Unformed genitalia	1	2.50
	Malformed penis	2	5.00
Defects of eye	**Sub-total (N)**	**2**	**100.00**
	Anophthalmia	1	50.00
	Congenital cataract	1	50.00
Defects of anus	**Sub-total (N)**	**2**	**100.00**
	Imperforate anus	2	100.00
All MESBDs	**Total**	**362**	**100.00**

MESBDs, Major External Structural Birth Defects

3.3.2 Prevalence of major external structural birth defects, 2014-2018

The prevalence estimates for defects of the musculoskeletal and central nervous systems ranged from 22.98 (95% CI: 11.87-40.13) to 116.90 (95% CI:92.98-145.08) per 100000 live births (LBs) and 13.40 (95% CI: 5.39-27.61) to 32.79 (95% CI: 20.79-49.19) per 100000 live births during the study period, respectively **(Table 3).**

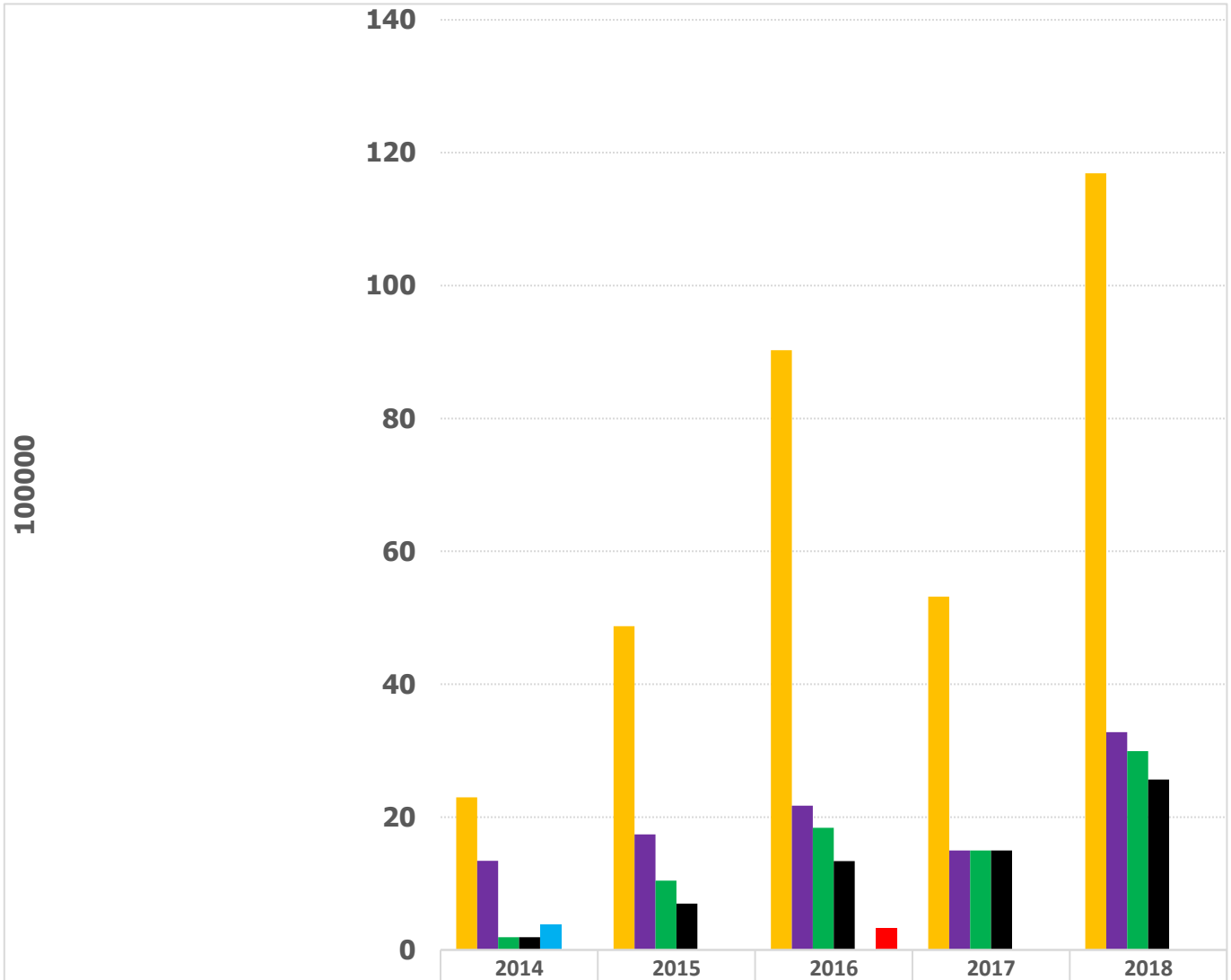
Table 3: Prevalence of MESBDs per 100000 live births in Kiambu County, 2014-2018

Year	Live births (N)	Groups of major external structural birth defects	Cases (n)	Prevalence/ 100000 LBs	95% Binomial Exact CI
2014	**52229**	Defects of the musculoskeletal system	12	22.98	11.87-40.13
		Defects of the central nervous system	7	13.40	5.39-27.61
		Orofacial defects	1	1.91	0.0485-10.67
		Defects of the genital organs	1	1.91	0.0485-10.67
		Defects of the eye	2	3.83	0.46-13.83
		Defects of the anus	-	-	-
		Annual prevalence per 100000 LBs	**23**	**44.04**	**27.92-66.07**
2015	**57456**	Defects of the musculoskeletal system	28	48.73	32.39-70.43
		Defects of the central nervous system	10	17.40	8.35-32.01
		Orofacial defects	6	10.44	3.83-22.73
		Defects of the genital organs	4	6.96	1.90-17.82
		Defects of the eye	-	-	-
		Defects of the anus	-	-	-
		Annual prevalence per 100000 LBs	**48**	**83.54**	**61.60-110.75**
2016	**59824**	Defects of the musculoskeletal system	54	90.26	67.82-117.76
		Defects of the central nervous system	13	21.73	11.57-37.16
		Orofacial defects	11	18.39	9.18-32.90
		Defects of the genital organs	8	13.37	5.77-26.35
		Defects of the eye	-	-	-
		Defects of the anus	2	3.34	0.41-12.08
		Annual prevalence per 100000 LBs	**88**	**147.10**	**117.99-181.20**
2017	**60198**	Defects of the musculoskeletal system	32	53.16	36.36-75.03
		Defects of the central nervous system	9	14.95	6.84-28.38
		Orofacial defects	9	14.95	6.84-28.38
		Defects of the genital organs	9	14.95	6.84-28.38
		Defects of the eye	-	-	-
		Defects of the anus	-	-	-
		Annual prevalence per 100000 LBs	**59**	**98.01**	**74.62-126.41**
2018	**70147**	Defects of the musculoskeletal system	82	116.90	92.98-145.08
		Defects of the central nervous system	23	32.79	20.79-49.19
		Orofacial defects	21	29.94	18.53-45.76
		Defects of the genital	18	25.66	15.21-40.55

		Defects of the eye	-	-	-
		Defects of the anus	-	-	-
		Annual prevalence per 100000 LBs	**144**	**205.28**	**173.15-241-64**
	299854	**Five-year prevalence per 100000 LBs**	**362**	**120.73**	**108.61-133.82**

LBs, Live Births; n, Numerator, N, Denominator; CI, Confidence Interval

The study similarly showed a remarkable variation in annual prevalence estimates of the six groups of major external structural birth defects **(Figure 2).**



	2014	2015	2016	2017	2018
Defects of the musculoskeletal system	22.98	48.73	90.26	53.16	116.9
Defects of the central nervous system	13.4	17.4	21.73	14.95	32.79
Orofacial defects	1.91	10.44	18.39	14.95	29.94
Defects of the genital organs	1.91	6.96	13.37	14.95	25.66
Defects of the eye	3.83				
Defects of the anus			3.34		

Figure 2: Bar chart for the prevalence of the six groups of MESBDs among children in Kiambu County, 2014-2018

3.3.3 Prevalence trend of major external structural birth defects, 2014-2018

There was a steady annual increase in the prevalence estimates of the six groups of major external structural birth defects ranging between 44.04 (95% CI: 27.92-66.07) in 2014 and 205.28 (95%

CI: 173.15-241.64) per 100000 live births in 2018, despite a slight decline observed in 2017 estimated at 98.01 (95% CI: 74.62-126.41) per 100000 live births **(Figure 3).**

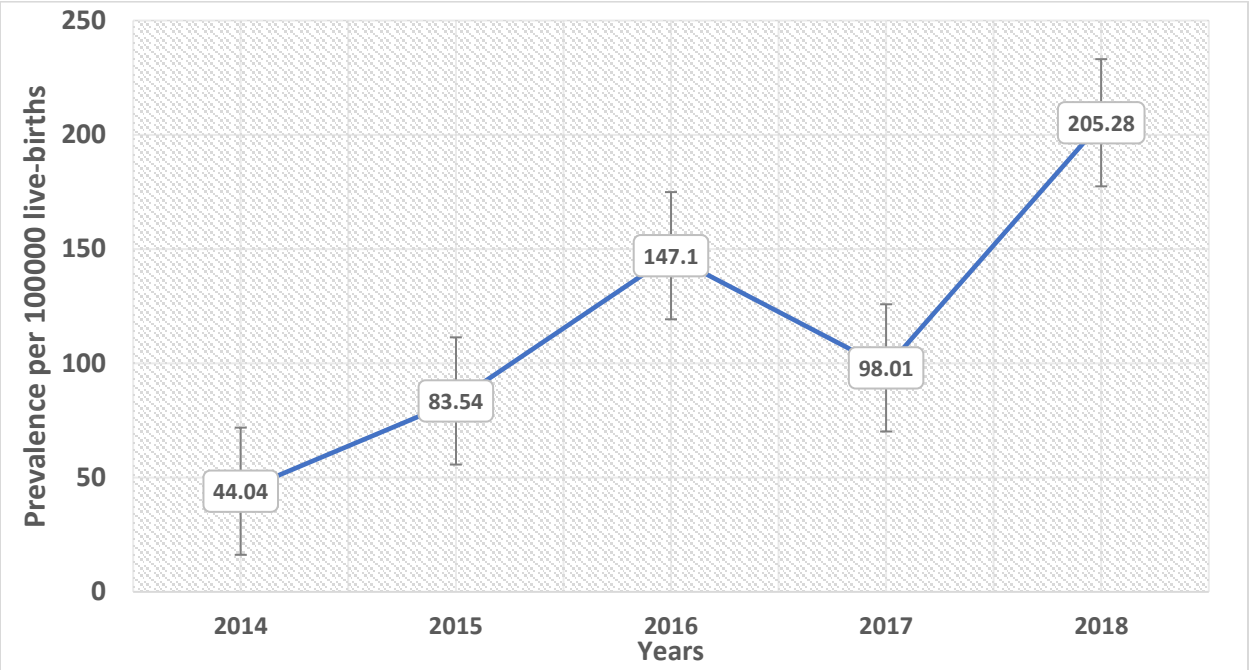
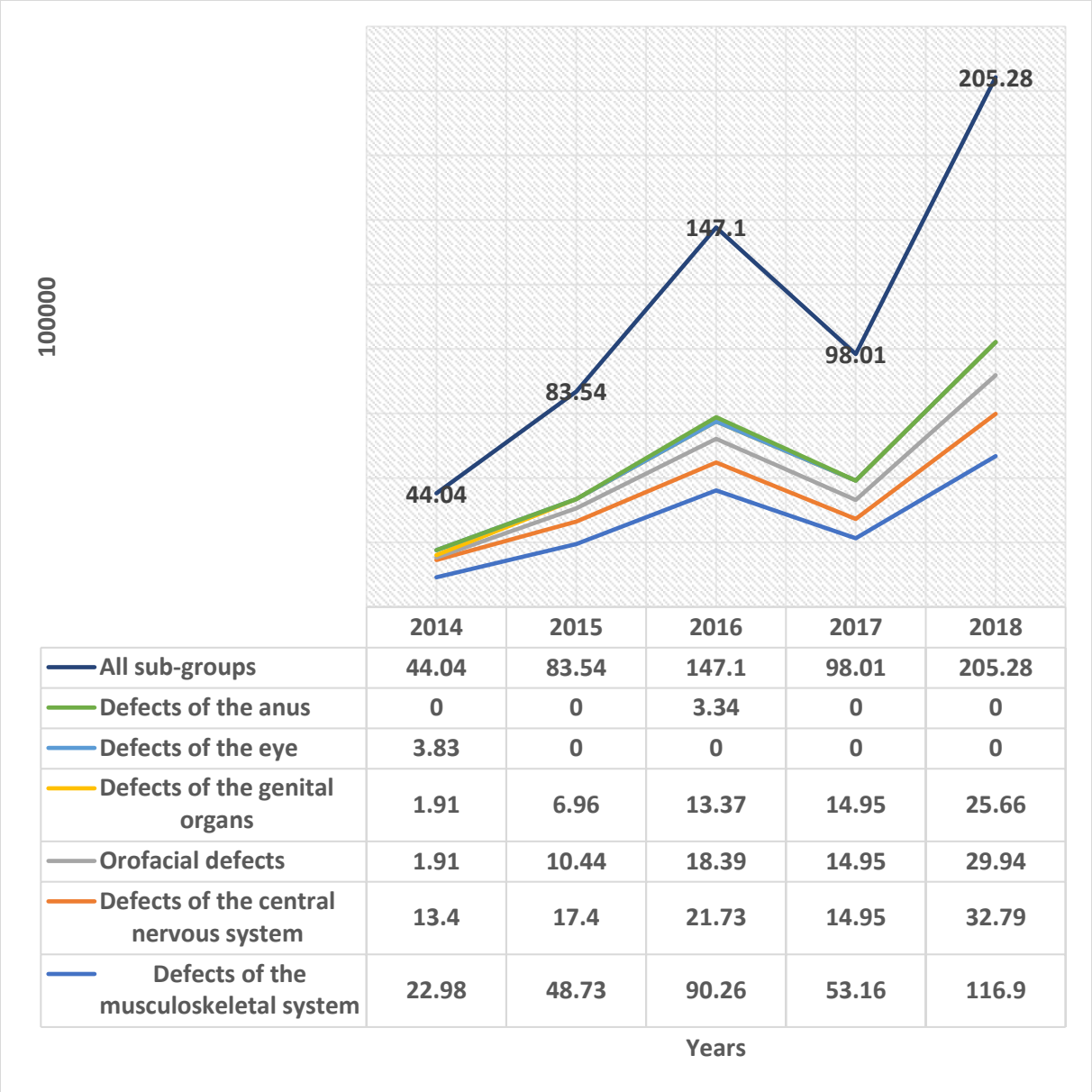


Figure 3: A line graph for the prevalence of the six groups of MESBDs among children in Kiambu County, 2014-2018

Collectively and individually all the six groups of birth defects were on an upward trajectory during the study period **(Figure 4).** This figure is not necessarily drawn to scale, however is meant to show prevalence trends of the six groups of the defects collectively and individually.



	2014	2015	2016	2017	2018
All sub-groups	44.04	83.54	147.1	98.01	205.28
Defects of the anus	0	0	3.34	0	0
Defects of the eye	3.83	0	0	0	0
Defects of the genital organs	1.91	6.96	13.37	14.95	25.66
Orofacial defects	1.91	10.44	18.39	14.95	29.94
Defects of the central nervous system	13.4	17.4	21.73	14.95	32.79
Defects of the musculoskeletal system	22.98	48.73	90.26	53.16	116.9

Figure 4: Line graphs for the prevalence of the six groups of MESBDs among children in Kiambu County, 2014-2018.

3.4 Discussions

The study observed six groups of MESBDs affecting the musculoskeletal system, central nervous system, orofacial organs, genital organs, ocular and anal organs, thus contributing to the worldwide empirical debate on MESBDs as a salient global problem awaiting explosion. The study observed 362 cases of these defects constituting 29 specific birth defects affecting the six body organ systems described above. Defects of the musculoskeletal and those of the central nervous systems were shown by this study as the most prevalent in Kiambu County. These findings were consistent

with the results of other studies carried out in the region, such as Ethiopia (Githuku et al., 2014; Liu et al., 2016; Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018; Moorthie, Blencowe, Darlison, Lawn, Mastroiacovo, et al., 2018; Muga et al., 2009; WHO, 2014, 2020). Congenital talipes equinovarus, cleft lip with palate hypospadias, limb defect reductions, anencephaly, hydrocephalus, and spina bifida were the most common defects among the 29 specific MESBDs in that order. A population-based study conducted between 2009 and 2010 in Kenya had similar observations encountering 35 cases of specific of MESBDs (Wu et al., 2013). Some of the cases encountered during that period consisted of a clubfoot, hypospadias, hydrocephalus, spina bifida/encephalocele, cleft lip, bladder exstrophy, and imperforate anus; observations similar to this study among other defects except bladder exstrophy (Wu et al., 2013).

Defects of the musculoskeletal systems were notably on a spiralling trajectory with an exceedingly high proportional contribution to the overall prevalence of MESBDs; this study observed almost two-thirds (57.46%) whereas as a study conducted in 1983-1984 reported one-third (33.9%) of the major external structural birth defects reported in a hospital-based study at Kenyatta National Hospital maternity unit between 1983-1984 (Muga et al., 2009). These findings point to possible increased exposure of women of reproductive age to teratogenic chemicals, and metals (pesticides, and teratogenic therapeutic medicines), multifactorial inheritance (parity, nature of pregnancy, siblings with a history of birth defects, and sex of the 'last-born' child), and/or sociodemographic-environmental risk factors (maternal age, educational level, and occupation) having been associated with the defects of the musculoskeletal system (Christianson et al., 2005, 2006; Edison & Muenke, 2004; Grossman, 1972; Kabubo-Mariara et al., 2012; Lucas et al., 2003; Wagstaff, 1986; Watkins et al., 2003). Because Kiambu is largely an agricultural county, there could be an increased likelihood of exposure to pesticide-related chemicals and metals among women of reproductive age.

Some studies have however reported defects of the central nervous system as the most common among MESBDs pointing to the ineffectiveness of public health intervention for prevention and control of such defects in other regions (Feldkamp et al., 2017; Sitkin et al., 2015). In Kenya, studies have shown a steady decrease in the prevalence of neural tube defects accounting for 28.6%

and 16.15% of all major external structural birth defects in 1984 and 2015, respectively (Muga et al., 2009). Similarly, a relatively low (17.13%) contribution of neural tube defects to MESBDs was observed in this study, further demonstrating a decline in the trend of neural tube defects locally. Increased preconception folic-serum levels are known to effectively prevent the occurrence of neural tube defects. Therefore, the decline in the prevalence of neural tube defects being observed could have been as a result of increased iron-folic acid supplementation by pregnant women in Kenya (Botto et al., 2004; Christianson et al., 2005, 2006; Hage et al., 2012; Taye et al., 2018, 2019; WHO, 2014, 2020). The trends of neural tube defects and other MESBDs could be reversed further if effective public health interventions are strictly implemented at least twelve weeks pre-conception and eight weeks post-conception.

Even though this study reported 29 specific types of the six groups of major external structural birth defects with musculoskeletal and central nervous defects as the most common among the groups in general, hypospadias (82.50%); a male genital organ defect was the most frequently occurring specific MESBDs among those of the genital organs. Although many studies have not been reporting findings on defects of genital organs, this study further showed epispadias; another defect of the male genital organ was similarly common in the county. This could be suggestive of a constant prevalence of the most common risk factors for hypospadias among other genital defects such as advanced maternal age beyond 35 years and BMI >26 (Watkins et al., 2003). Notably, cleft lip with the palate (77.08%) and cleft lip without palate (14.58%) were the most common specific MESBDs of the orofacial clefts in the county. This also mimicked findings of other studies showing cleft lip with the palate and cleft lip without palate as the most prevalent defects among orofacial clefts (Agbenorku, 2013; Onyango & Noah, 2005) Similarly, this study reported congenital talipes equinovarus (73.08%) as the most common among major external structural birth defects of the musculoskeletal system; an observation corroborated by other study findings regionally and globally (Christianson et al., 2005, 2006; Muga et al., 2009; WHO, 2014, 2020). Congenital talipes equinovarus develop quite early in gestation and affects the structures and positions of the foetal feet (Tracey Smythe et al., 2017). Remarkably, limb reduction defects were observed in this study as the second most common among musculoskeletal system defects, however, the locally existing empirical literature has not been reporting proportions of such defects.

Anencephaly (30.65%), and hydrocephalus (25.81%) were observed as the first two most common defects of the central nervous system in Kiambu County. Although other study findings reported hydrocephalus as the most commonly occurring neural tube defect followed by spina bifida and encephalocele; anencephaly emerged as the most prevalent among neural tube defects in this study (Wu et al., 2013). Similarly, this study noted a decrease in cases of encephalocele (3.23%) (Wu et al., 2013). Anencephaly is a highly fatal neural tube defect known to significantly contribute to prenatal deaths and lead to few live births with anencephaly, however, this was not the case in this study (Christianson et al., 2005, 2006; Gedefaw et al., 2018; Githuku et al., 2014; Munyi, Poenaru, Bransford, & Albright, 2009; WHO, 2014, 2020). Instead, many cases of anencephaly were observed pointing to the possible increased prevalence of risk factors specific to anencephaly and not neural tube defects in its entirety. This phenomenon underpins further research endeavours to determine risk factors specific to the intrauterine formation of anencephaly rather than other forms of neural tube defects, and the importance of routine autopsies on all stillbirths to establish the causes of such deaths for purposes of improving prevalence estimations of major external structural birth defects.

Certain limitations were however noted during the study period; first and foremost, there were inadequate stores and shelves for the medical records leading to heaped pools of records not necessarily arranged in an ordered manner, and sometimes leading to defaced records. Secondly, medical records used in this study were not designed for epidemiological studies, therefore, researchers perused over many pages of maternity files to identify summary sections of the files where major external structural birth defects were defined, referenced, or described. Additionally, although the files were accessible in the third county referral hospital, summary sections of maternity files for recording major external structural birth defects were missing, therefore no records were abstracted for the five-year study period in this facility. In 2017, maternity files in one of the county referral hospitals were not accessed because they were relocated to an unknown place within the hospital, explaining a decline in prevalence estimates observed **(Figure 4).** Further, cases described as congenital anomalies, gross congenital anomalies, and multiple congenital anomalies were excluded as part of the study numerator because I was unable to distinguish them for categorization into the six groups and sub-groups of the major external structural birth defects. Stillbirths were also ineligible for inclusion in the study because their

causes were unknown to the researchers. The factors described above certainly contributed to underestimations and variations of the prevalence estimates of major external structural birth defects in the county.

3.5 Conclusions and recommendations

This was the first study to estimate a region-specific prevalence of MESBDs in Kenya. Despite the limitations of the study and the fact that defects of the musculoskeletal, central nervous system were the most frequent groups of MESBDs, hypospadias; a defect of the male genital organ was also common among the 29 sub-groups of the defects in the county. Although anencephaly is the leading cause of stillbirths associated with severe birth defects, it was among the most prevalent among the sub-groups of MESBDs among live births, and the highest among defects of the central nervous system. The study showed a spiralling trajectory of MESBDs during the five-year study period. This observation pointed at the possibility of constant exposure to women of reproductive age to potential risk factors for a myriad of MESBDs. In the absence of effective prevention and control measures, accessible corrective, and rehabilitative services for MESBDs; adverse health effects, psychosocial impacts, developmental challenges, and reduced economic productivity arising from lifelong disabilities are inevitable. Establishing county-specific and national surveillance systems for MESBDs would be of great public health importance in understanding the public health magnitude of these defects, regionally and nationally. Lastly, we recommend that future studies should investigate risk factors for MESBDs in Kiambu County with a view of cascading similar studies across the country for purposes of informing designs and formulations of defect-specific surveillance, prevention, and control strategies.

CHAPTER FOUR: RISK FACTORS FOR MAJOR EXTERNAL STRUCTURAL BIRTH DEFECTS AMONG CHILDREN IN KIAMBU COUNTY, KENYA: A CASE-CONTROL STUDY

Abstract

Introduction: Although major external structural birth defects continue to occur globally, the greatest burden is shouldered by resource-constrained countries with no surveillance systems. To my knowledge, many studies have been published on risk factors for major external structural birth defects, however, limited studies have been published in developing countries. The objective of this study was to identify the risk factors for major external structural birth defects among children in Kiambu County, Kenya.

Methods: A hospital-based case-control study was used to identify the risk factors for major external structural birth defects. A structured questionnaire was used to gather information retrospectively on maternal exposure to environmental teratogens, multifactorial inheritance, and sociodemographic-environmental factors during the study participants' last pregnancies. Descriptive analyses (means, standard deviations, medians, and ranges) were used to summarize continuous variables, whereas categorical variables were summarized as proportions and percentages in frequency tables. Afterward, logistic regression analyses were conducted to estimate the effects of the predictors on the odds of major external structural birth defects.

Results: Women who conceived when residing in Ruiru sub-county (adjusted odds ratio [aOR]: 5.28; 95% CI: 1.68-16.58; P<0.01), and Kiambu sub-county (aOR: 0.27; 95% CI; 0.076-0.95; P =0.04); and preceding siblings with history of birth defects (aOR: 7.65; 95% CI; 1.46-40.01; P =0.02) were identified as the significant predictors of major external structural birth defects in the county.

Conclusions: These findings pointed to MESBDs of genetic, multifactorial, and sociodemographic-environmental etiology. Thus, I would like to recommend regional defect-specific surveillance programs, public health preventive measures, treatment strategies, and research to understand the epidemiology and economic burden of these defects in Kenya. Further, I recommend specifically the integration of clinical genetic services with routine reproductive health services because of potential maternal genetic predisposition in the region.

Keywords: Major external structural birth defects, risk factors, case-control study, county, Kenya

4.1 Introduction

Worldwide, an estimated 7.9 million children are born every year with a birth defect, of which around 3.3 million die before age five and about 3.2 million could be physically disabled for life (Christianson et al., 2005, 2006; WHO, 2014, 2020). More than 94% of such defects occur in developing countries where approximately 95% of these children do not survive beyond childhood (Christianson et al., 2005, 2006). Birth defects are defined as abnormalities of body structures or functions that develop during the organogenesis period (first trimester of gestation) and are detectable during pregnancy, at birth, or soon after (Sever, 2004; WHO, 2014, 2020). These defects may be classified as major when associated with significant adverse health effects requiring medical/surgical care; otherwise, they are described as minor (Christianson et al., 2005, 2006; WHO, 2014, 2020). Alternatively, they can be classified as external when visible at birth or soon after; or internal when advanced medical imaging techniques are required for their detection (Moorthie, Blencowe, Darlison, Lawn, Morris, et al., 2018; Parker et al., 2010; Tinker et al., 2015). Consequently, the phrase 'major external structural birth defects' (MESBDs) denotes congenital physical abnormalities that are clinically obvious at birth or soon after which are associated with significant adverse health effects and calling for medical and/or surgical interventions (Christianson et al., 2005, 2006; WHO, 2014, 2020).

The causes of these defects can be classified into three categories: (i) identifiable environmental factors (teratogens and/or micronutrient deficiencies); (ii) identifiable genetic factors (single-gene defects and/or chromosomal abnormalities); and (iii) complex genetic and idiopathic environmental factors, described as a multifactorial inheritance (Christianson et al., 2005, 2006; Feldkamp et al., 2017; Feldkamp et al., 2015; Khurmi et al., 2014; Lucas et al., 2003; Penchaszadeh, 2002; Tinker et al., 2015). One-third of these causes are attributed to identifiable environmental and genetic factors, whereas the rest are believed to be of multifactorial etiology (Christianson et al., 2005, 2006; Feldkamp et al., 2017; Feldkamp et al., 2015; Khurmi et al., 2014; Lucas et al., 2003; Penchaszadeh, 2002; Tinker et al., 2015). Additionally, the environmental endowment of women of reproductive age is thought to operate through their socioeconomic and sociodemographic characteristics described as sociodemographic-environmental causes of MESBDs (Christianson et al., 2005, 2006; Feldkamp et al., 2017; Feldkamp et al., 2015; Khurmi et al., 2014; Lucas et al., 2003; Penchaszadeh, 2002; Tinker et al., 2015).

Organogenesis occurs in the first eight weeks of gestation; however, approximately half of pregnancies are usually unplanned/unintended, thus not recognized until the end of the second trimester formed (Christianson et al., 2005, 2006; Finer & Zolna, 2014, 2016; Taye et al., 2018, 2019; Tinker et al., 2015). Completing more years of education could improve maternal health because educated women are more likely to make informed reproductive health choices than those with low levels of education to improve the birth outcomes (Fraser et al., 1995; Grossman, 1972; Ochako et al., 2011; Wagstaff, 1986). Some of the notable maternal decisions include planned pregnancy, preconception folic acid intake in anticipation of conception, and subsequently prompt prenatal care (Bello et al., 2013; Christianson et al., 2005, 2006; Gedefaw et al., 2018; Grossman, 1972; Hage et al., 2012; Kabubo-Mariara et al., 2012; Tsehay et al., 2019; Wagstaff, 1986). Supplemental vitamins with folic acid are dispensed during routine antenatal care (ANC) visits as well as health education on adequate nutrition, avoidance of environmental teratogens, and maternal infections as public health preventive strategies for MESBDs (Florentina Mashuda, 2014; Penchaszadeh, 2002). These measures could be effective only when pregnant women promptly began ANC within eight weeks of gestation before the intrauterine formation of MESBDs (Tinker et al., 2015). Folic acid is essential for normal development of the brain and spinal cord during the first four weeks of conception, and have been found to reduce the occurrence of neural tube defects, orofacial clefts, limb reduction defects, urinary system defects, and omphalocele; some of the most prevalent defects in the county (George Nyadimo Agot, Mweu, & Wang'ombe, 2020; Godwin et al., 2008; Salerno, 2009). Notably, folic acid is useful in the prevention of some defects of post-conception origin because the intrauterine formation of these defects usually occurs within eight weeks of gestation (Christianson et al., 2005, 2006; Godwin et al., 2008; Salerno, 2009). Thus, the recommended first ANC at the 12^{th} week of pregnancy could be a sub-optimal preventive strategy for these defects, nevertheless, it improves the experiences of the women during pregnancy and childbirth (WHO, 2018).

Maternal occupation as a predictor of MESBDs could be dependent on educational levels nonetheless some occupations such as farming could expose women of reproductive age to teratogenic pesticides (Pašková et al., 2011). Similarly, maternal residence at conception leads to the intrauterine formation of MESBDs determined by environmental etiology attributed to widespread poverty, environmental pollution, inadequate health care services, and ineffective

preventive strategies; factors largely found in developing countries (Christianson et al., 2005, 2006; Lucas et al., 2003).

Parental age is a multifaceted risk factor whose mechanisms of actions in the intrauterine formation of these defects are underpinned by the human biology and sociodemographic characteristics among women of reproductive age. From the biological standpoint, the female gametogenesis begins before birth with the initial meiotic division (prophase stage) expected to complete shortly before ovulation, however, this is not the case always because the process may delay up to 45 years to conclude (Florentina Mashuda, 2014). Thus, the oocytes take exceedingly long in the prophase stage increasing the likelihood of meiotic errors due to exposure to the environmental teratogens (Florentina Mashuda, 2014). Advancing maternal age beyond 35 years is similarly a risk factor for MESBDs of genetic etiology due to chromosomal abnormalities (Florentina Mashuda, 2014; Moore et al., 2018; Shawky & Sadik, 2011). Similarly from the biological viewpoint, genetic mutations and accumulation of chromosomal aberrations during maturation of male germ cells have been attributed to the formation of MESBDs in utero (Barker et al., 2003; Bray et al., 2006). The amount of deoxyribonucleic acid damage in sperm of men aged 36-57 is three times that of men <35 years, also increasing the likelihood of these defects in aging couples (Bray et al., 2006; Yang et al., 2007). From the sociodemographic perspective, parental age could be associated with MESBDs of multifactorial etiology ascribed to physiological interactions between complex genetic, and idiopathic environmental attributes of women of reproductive age (Christianson et al., 2005, 2006; Lucas et al., 2003; WHO, 2014, 2020).

To my knowledge, many studies on the risk factors have been published in developed countries, however, such publications are scanty in developing countries owing to the rarity of MESBDs, unplanned/unintended pregnancies, and difficulties in identifying these women until the end of the second trimester when the defects have already formed (Tinker et al., 2015). To address this gap, this study investigated maternal periconceptional exposure to environmental teratogens, multifactorial, and sociodemographic-environmental risk factors for MESBDs in Kiambu County, Kenya. The study assessed: maternal periconceptional exposure to farm-sprayed pesticides, and teratogenic therapeutic medicines proxied by maternal chronic illnesses (epilepsy, hypertension, and diabetes mellitus); multifactorial inheritance proxied by the history of siblings with birth

defects, sex of the last-born 'current' child, nature of pregnancy, and parity; and sociodemographic-environmental factors consisting of parental age, residence, level of education, occupation, and adequate prenatal care proxied by gestational age, preconception folic acid intake and the trimester of first antenatal care. The findings of this study could provide great public health opportunities for the formulation of specific treatment strategies, preventive measures, risk-based surveillance systems, and clinical genetic services for the most prevalent MESBDs regionally and nationally. Consequently, the objective of this study was to identify the risk factors for MESBDs among children in Kiambu County, Kenya.

4.2 Methods

4.2.1 Study design and settings

A hospital-based case-control study was conducted to identify the risk factors for MESBDs in Kiambu County. The study participants were recruited as they presented to the child welfare clinics, neonatal/pediatric units, and occupational clinics for care during the data collection period from May 31^{st,} 2019, to July 31^{st,} 2019. A case-control design was the optimal design for this study considering its suitability for the investigation of rare outcomes, as is the case with MESBDs. Even though a population-based design would have been preferable, the ease of recruiting case and control subjects within the hospital settings favoured the hospital-based design. This was an observational study, therefore was reported as per the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines (Cuschieri, 2019; Da Costa et al., 2011).

The study was conducted in thirteen hospitals comprising three-county referral hospitals (Kiambu, Gatundu, and Thika), eight sub-county hospitals (Karuri, Kihara, Wangige, Nyathuna, Lari-Rukuma, Tigoni, Lussigetti, and Kigumo), and two faith-based hospitals (Presbyterian Church of East Africa Kikuyu Orthopaedic and African Inland Church Cure International) situated within Kiambu County, Kenya. The researcher was however denied entry to AIC Kijabe hospital despite requesting permission to be among the three faith-based hospitals for providing care to children born with major external structural birth defects in the county. Notably, neither population-based nor hospital-based surveillance systems for MESBDs existed in the county nor the study hospitals. Nonetheless, cases detected by primary health providers during childbirth and neonatal care were recorded for the compilation of monthly hospital reports and subsequent entry into the District Health Information System (DHIS). The cases were drawn from Kiambu, Thika, Gatundu, Tigoni,

Kikuyu, and Cure hospitals which provided occupational and rehabilitative health services to children with MESBDs. The controls, on the other hand, were drawn from Kiambu, Gatundu, Thika, Karuri, Kihara, Wangige, Nyathuna, Lari-Rukuma, Tigoni, Lussigetti, and Kigumo hospitals which provided child welfare services to the under-fives.

Kiambu is the second-most densely inhabited county with an estimated population of 2.4 million people out of an estimated national population of 47.5 million (KNBS, 2019). Its economic mainstay is largely agriculture, comprising tea, coffee, and dairy farming (KNBS, 2019). Of the county's total estimated population, approximately 2.2% aged ≥5 years are living with lifelong disabilities credited to major external structural birth defects (KNBS, 2019; Mugoya & Mutua, 2015). A study carried out in the county between 2014 and 2018 observed defects of the musculoskeletal system as the most prevalent single system defects followed by central nervous, orofacial clefts genital, ocular, and anal organ defects (George Nyadimo Agot et al., 2020).

4.2.2 Study population, and eligibility of participants

The study population consisted of children aged ≤5 years old seeking health services at the study hospitals during the study period spanning from 31st May to 31st July 2019. All children whose mothers consented to participate in the study were recruited.

4.2.3 Case definition and recruitment

Cases were defined as children aged ≤5 years born with at least one MESBDs to resident women of Kiambu County and seeking health care services at the neonatal units, paediatric wards, child welfare clinics, and/or occupational therapist clinics of the study hospitals during the two-month study period. The Research Assistants (RAs) liaised with team leads of the departments listed above to identify cases of MESBDs. The team leads had been working in these departments thus were conversant with the cases seeking services. The team leads invited the mothers of the children who met the case definition to comfortable private rooms within the departments where the study objectives were introduced to the caregivers, informed consents sought, and face-to-face interviewer-administered questionnaires conducted by the RAs. Because of the rarity of MESBDs, all cases that met the definition were purposively selected and whose caregivers consented to participate in the study were prospectively recruited and frequency-matched to the controls by the days of presentation until the required sample size was attained ***(see sample size determination).***

4.2.4 Control definition and recruitment

Controls were defined as children aged ≤5 years born without any forms of birth defects to resident women of Kiambu County and attending routine child welfare clinics at the study hospitals during the two-month study period. The Research Assistants liaised with team leads of the child welfare clinics to identify the children without any form of birth defects and were seeking routine immunization, and growth monitoring services. The team leads had been working in these clinics, hence were familiar with most of the under-fives seeking the services. These services are provided between 8.00 am and 5.00 pm from Monday to Friday; the team leads introduced the RAs who then briefed the potential participants on the study objectives. The number of cases recruited determined the number of controls for frequency matching in the ratio of 1:3 by the days of presentation respectively. However, because of the relatively large number of controls available, they were selected by simple and systematic random sampling techniques. The first control subjects were selected using sealed envelopes whereas the subsequent control subjects were selected using determined sampling intervals upon definition of the sample populations by the days of presentation. Informed consent was sought from each of the study participants who met the study eligibility criteria, and those who consented to participate in the study were prospectively recruited and administered face-to-face interviewer questionnaires in secluded comfortable rooms within the child welfare clinics till the desired sample size was achieved ***(see sample size determination).***

4.2.5 Sample size determination

The sample size was estimated as per the Kelsey JL *et al.* (Kelsey, Whittemore, Evans, & Thompson, 1996) formula specified for case-control studies as follows: -

$$n_1 = \frac{\left(Z_\alpha + Z_\beta\right)^2 \overline{pq}\,(r+1)}{r(p_1 - p_2)^2} \quad \textbf{Equation (2)}$$

$$\overline{q} = 1 - \overline{p}$$

$$n_2 = rn_1$$

$$p_1 = \frac{p_2 OR}{1 + p_2\,(OR - 1)}$$

$$\overline{p} = \frac{p_1 + rp_2}{r+1}$$

Where: n_1 is the number of cases and n_2 is the number of controls; p_1 is the proportion of cases whose caregivers did not begin prenatal care in the first trimester (primary exposure), p_2 is the proportion of controls whose caregivers did not begin prenatal care in the first-trimester set at 57% (Finer & Zolna, 2014, 2016). Remarkably, $Z_{\alpha/2}$ (1.96) and Z_{β} (-0.84) are the values specifying the desired two-tailed confidence level (95%) and statistical power (80%), respectively. The odds ratio *(OR)* for the effect of the primary exposure (cases whose caregivers did not begin prenatal care in the first trimester) was hypothesized to be 2.0 (universally accepted). The ratio *(r)* of unexposed to exposed individuals was set at 3.0, and given the estimates, a total sample size of 408 participants was derived (102 cases, and 306 controls).

4.2.6 The outcome and explanatory variables

The outcome (response) variable of interest was described as any type of "major external structural birth defects" observed during the data collection period. The explanatory (predictor) variables on the other hand consisted of environmental teratogens comprising farm-sprayed pesticides, and teratogenic medicines; multifactorial-inheritance consisting of nature of pregnancy, history of siblings with birth defects, and sex of the 'last-born' (current) child; and sociodemographic-environmental factors comprising maternal age, paternal age, maternal residence at conception, maternal level of education level, maternal occupation, gestational age (weeks) at first ANC visits, ANC began 8 weeks post-conception and preconception folic acid intake. The outcome variable as well the predictor variables were assessed as shown in the table below **(Table 4).**

Table 4: Study variables and their assessments

Variable (type)	**Method of assessment**	**Literature source**
Major external structural birth defects **(nominal)**	Major external structural birth defects (MESBDS) considered as the response variable was captured as "yes" for the children under five years born with MESBDs to resident women of Kiambu County (cases) and "no" for the children under five years who were not born with any form of birth defects to resident women of Kiambu County.	Maternal exposure to potential risk factors consisting of environmental teratogens, and sociodemographic-environmental factors increase the risk of intrauterine development of MESBDs (Christianson et al., 2005, 2006).

Exposure to sprayed farms pesticides **(nominal)**	Captured as "yes" for those who sprayed farms with pesticides and "no" for those who did not spray farms with pesticides	Exposure to teratogenic agents has been associated with abnormal embryology (Mlčáková et al., 2011; Pašková et al., 2011).
Teratogenic therapeutic medicines for chronic illnesses **(nominal)**	Captured as a nominal variable, categorized into three groups, and labelled as: 1= "medicines for hypertension", 2= "no medicines for chronic illnesses", and 3= "medicine for other chronic illnesses".	Exposure to the teratogenic agents could lead to mutations of the deoxyribonucleic acid (DNA) causing the intrauterine formation of MESBDs (Christianson et al., 2005, 2006).
ANC began 8 weeks post-conception **(nominal)**	Captured as yes/no	Prompt access and utilization of antenatal care influences intake of supplemental iron and folic acid, thus improving the accumulation of maternal serum folate (Hage et al., 2012; Ochako et al., 2011).
Gestational age (weeks) at first ANC **(continuous)**	Captured as a continuous variable measured in weeks by computing the difference between the dates of first antenatal visits and dates of last menstrual period of the last pregnancies drawn from the antenatal care booklets, categorized into two groups, and labelled as: 1<9 weeks, and 2 ≥ 9 weeks	Prompt access and utilization of antenatal care influences intake of supplemental iron and folic acid, thus improving the accumulation of maternal serum folate (Hage et al., 2012; Ochako et al., 2011).
Preconception folic acid intake **(nominal)**	Captured as yes/no	Serum folate accumulation plays a significant responsibility in single-carbon transfer reactions and many metabolic pathways including the synthesis of purines and pyrimidines (proteins) underlying the formation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (Manning Feinleib, 2001; Salerno, 2009).
Sex of the last-born 'current' child **(nominal)**	Entered as male or female	Various types of MESBDs have been associated with particular sex of children (Cui et al., 2005; KNBS, 2019).
History of siblings with birth defects **(nominal)**	This was captured as yes/no	Familial history of certain MESBDs has been associated with recurrence and emergence of

		particular defects among siblings (El Koumi, Al Banna, & Lebda, 2013; Florentina Mashuda, 2014).
Parity **(continuous)**	Abstracted from the antenatal booklets as a continuous variable, categorized into two groups and labelled as: 1= "primiparous", and >1= "multiparous"	Multiparity has been associated with the occurrence of MESBDs among women of reproductive age (Duong et al., 2012; Jawad, Haq, & Cheema, 2017).
Nature of pregnancy **(nominal)**	Entered as single or multiple	Multiple pregnancies have been observed to increase the risk of the occurrence of MESBDs compared to singleton pregnancies (Tang et al., 2006).
Maternal age **(continuous)**	Captured in years, categorized into five groups, and labelled as: 1<20, 2=20-29, 3=30-39, 4=40-49, and 5>49 years, and recategorized into two groups and labelled as: 1<35, and 2≥35 years	Women aged at least 35 years have previously been reported to have an increased likelihood of giving birth to children with structurally malformed infants (Hollier, 2000).
Paternal age **(continuous)**	Captured in years, categorized into seven groups, and labelled as: 1=20-24, 2=25-29, 3=30-34, 4=35-39, 5=40-44, 6=45-49, and 7>49 years, and recategorized into two groups and labelled as: 1<35, and 2≥35 years	Males aged at least 35 years have previously been associated with an increased likelihood of defect-affected pregnancies/births in their female counterparts (Bray et al., 2006).
Level of education **(ordinal)**	Captured as no schooling, primary, secondary, college certificate, college diploma, and university degree, categorized into three groups and labelled as: 1≤ primary, 2=secondary, and 3=tertiary	Tertiary maternal education level would be expected to positively influence the reduction of birth defects because of maternal increased knowledge on the risk factors (Grossman, 1972, 1999).
Maternal occupation **(nominal)**	Captured as a nominal variable, and categorized into three groups, and labelled as: 1=farming, 2=employed, and 3=unemployed.	Teratogen-exposing occupations could also lead to the intrauterine formation of MESBDs (Mlčáková et al., 2011; Pašková et al., 2011).
Maternal residence **(nominal)**	Captured as a nominal variable, and categorized into five groups, and labelled as: 1=Thika, 2=Gatundu, 3=Kiambu, 4=Ruiru, and 5=other sub-counties	Maternal residence contributes to the public health magnitude of MESBDs due to the prevalence of environmental and genetic factors (Christianson et al., 2005, 2006).

ANC, Antenatal Care; MESBDs, Major External Structural Birth Defects

4.2.7 Conceptual framework

The conceptual framework depicting the predictor-outcome relationship was organized based on the three causal categories of MESBDs consisting of multifactorial inheritance, environmental teratogens, and sociodemographic-environmental factors illustrated in **Figure 5.** Notably, assessment of effects of the genetic factors sufficed in this study as multifactorial etiology to measure maternal genetic predispositions because of the scientific limitation of observational in disentangling genetic etiology of MESBDs.

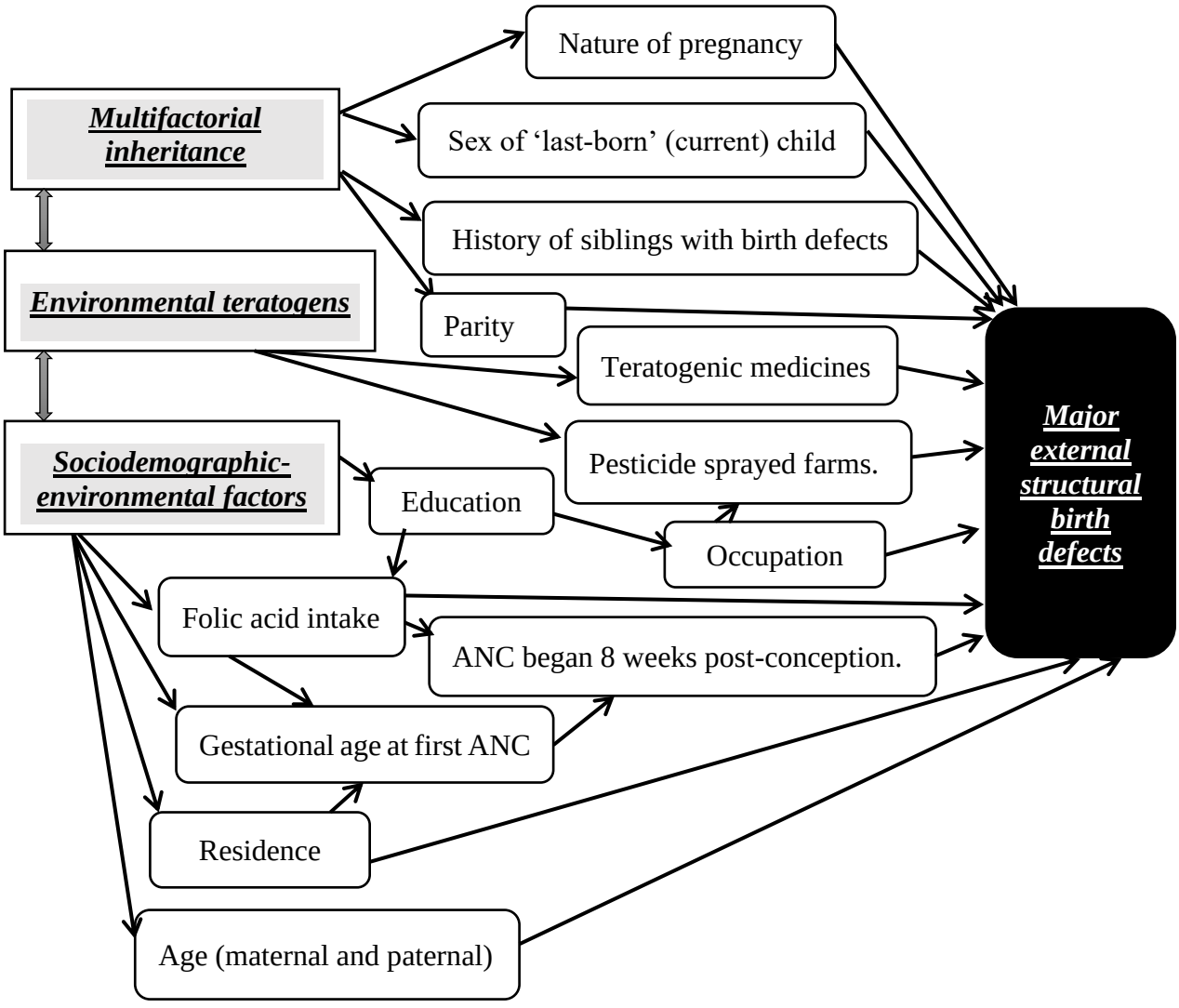


Figure 5: Causal diagram of factors thought to influence MESBDs among children in Kiambu County, Kenya.

4.2.8 Specifications of the study model

Theoretically, this phenomenon described in the conceptual framework above **(Figure 5)** could be described as maternal health production function and specified by (Grossman, 1972, 1999; Wagstaff, 1986) as: -

$$\boldsymbol{H = F(X)} \qquad \textit{Equation (3)}$$

Where, H measured individual maternal health output whereas X was a vector of the individual maternal inputs to the health production functions $\boldsymbol{F}$ (Fayissa & Gutema, 2008; Fayissa* & Gutema, 2005). The elements of the vector consisted of the factors described in the conceptual framework above as environmental teratogens, multifactorial inheritance, and sociodemographic-environmental predictors of the occurrence of major external structural birth defects **(Figure 5)**. These postulations could be expressed mathematically in multiple linear regression models structurally stated generally as:

$$\mathbf{Y=\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots\ldots + \beta_K X_K + \varepsilon.} \qquad \textit{Equation (4)}$$

Where, Y, was the outcome/dependent variable, X's, were the independent variables, β's, were the partial slope coefficients of the parameters, and ε was the stochastic error term. From population regression function (PRF) expressed in equation (4), a sample regression function (SRF) was expressed as: -

$$\mathbf{y=\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots\ldots + \beta_K X_K + \varepsilon.} \qquad \textit{Equation (5)}$$

The regression function, $\boldsymbol{\beta_0 + \beta_1 X_1 + \beta_2 X_2}$ gave the explained variations in the outcome variables, whereas stochastic/random error term **ε** gives the unexplained variations in the outcome variables resulting from natural/biological variation among observational units, measurement error in the response variable, and other extraneous factors influencing the response, for example, unknown confounders illustrated in the conceptual framework.

Given the observations made in the conceptual framework above, the model specified here was stated as a binomial logistic regression model. The occurrence of specific major external structural birth defects was hypothesized to depend on environmental-teratogens, multifactorial-inheritance, and sociodemographic-environmental factors analysed using a logistic regression model. The logistic regression model was expressed as:

$$P(y=1|x) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots\ldots + \beta_K X_K. \qquad \textit{Equation (6)}$$

Where, y, was the binary outcome/dependent variable taking the values zero and one, X's, were the independent variables, β's, were the partial slope coefficients of the parameters, and ε was the stochastic error term. It would always be true that P(y=1|x) = E(y|x) in a binary logistic regression model expressed above.

4.2.9 Assumptions of the analysis

The assumptions for this study consisted of linearity referring to the linear relationship between the variables, independent paired observations, homoscedasticity implying the variance of the subpopulations is equal, the independent variables are measured without error (fixed and discrete), and normality (the error term is normally distributed with μ=0 and a variance, σ).

4.2.10 Data collection process and study variables

Before data collection, four nursing graduate interns were recruited and trained as RAs on sound interviewing techniques, and information derivation/validation from ANC booklets. This was to ensure the data collection process spanning two months (May 31st to July 31^{st,} 2019) was conducted in a standardized manner. The ANC booklet contains maternal profile, medical/surgical history, previous pregnancy history, clinical notes, and physical examination findings on ANC visits, among others. The maternal profile includes name, age, parity gravidity, height, weight, last menstrual period (LMP), expected date of delivery (EDD), and date of first ANC visit. Face-to-face structured questionnaires were administered to the mothers of the study participants by RAs in comfortable secluded rooms within neonatal units and occupational therapy clinics for cases, and child welfare clinics for the controls. Data were gathered retrospectively on exposures to environment-teratogens (farm-sprayed pesticides, and teratogenic medicines proxied by chronic illnesses such as epilepsy, hypertension, diabetes mellitus), multifactorial inheritance (parity, nature of pregnancy, history of siblings with birth defects, and sex of the 'last-born' (current) child; and sociodemographic-environmental factors (maternal age, paternal age, residence, education level, occupation, and adequate prenatal care proxied by gestational age and preconception folic acid intake).

4.2.11 Ethical approvals, authorizations, and considerations

Ethical approval was obtained from Kenyatta National Hospital (KNH)-University of Nairobi (UoN) Ethics Review Committee (Ref. No: KNH-ERC/A/44). The National Commission for Science, Technology, and Innovation further granted us permission vide a letter Ref. No:

NACOSTI/P/19/75586/28325 to collect data in Kiambu County. The County Commissioner of Kiambu also provided an authorization Ref. No: ED.12 (A)/1/VOL.11/107 and copied to the County Director of Education who acknowledged by stamping the letter. The County Director of Health, Kiambu County similarly authorized this study to vide a letter Ref. No: KIAMBU/HRDU/AUTHO/2019/03/06/AgotGN. The study was conducted in 13 hospitals (3 county referral hospitals, 8 sub-county hospitals, and 2 faith-based hospitals) which granted additional permissions through written authorizations or counter approving the authorization letter issued by the County Health Directorate. The Medical Superintend of Thika county referral hospital authorized the study to vide a letter Ref. No. MOMS/TKA/VOL.III (728), whereas Gatundu county referral hospital issued an authority vide a letter Ref: GTD/GEN/37/VOL.1/97. The Medical Director of AIC International hospital-Kijabe issued an authorization through the Research Board (IRB) of the hospital, whereas the Medical Director of PCEA Kikuyu hospital granted the permission after a written commitment by the Principal Investigator (PI) to submit the report of the study upon completion. The purpose of the study was explained to participants and written informed consent was obtained from mothers of the study subjects before engaging them in the study and subsequently administering the face-to-face structured interviewer questionnaires. The data collected were de-identified using anonymous codes and entered in a laptop secured by an alphanumeric coded key only known to the PI to maintain confidentiality.

4.2.12 Minimization of biases

Considering potential biases inherent in case-control studies likely to invalidate the study results, deliberate attempts were made to minimize their occurrence. First and foremost, the research assistants were trained on sound interviewing techniques and information derivation/validation from ANC booklets to minimize interviewer and information biases, respectively. In a bid to minimize recall bias, gestational age at the first ANC was estimated from the dates of the last menstrual period and dates of the first ANC that were obtained from the ANC booklets.

4.2.13 Data processing and statistical analysis

Following data collection, filled questionnaires were manually checked daily for accuracy and completeness and subsequently entered in a Microsoft Excel spreadsheet (Microsoft Office Professional Plus 2019) by two independent data managers to reduce potential errors. The excel dataset was validated and exported to Stata software version 14.0 (Stata Corporation, Texas, USA) for further cleaning, coding, and analyses. Descriptive analyses (means, medians, standard

deviations, and ranges) were used to summarize continuous variables, whereas proportions and percentages for categorical variables were generated and presented in frequency tables. Afterward, the effect of each predictor on the odds of MESBDs was assessed using univariable logistic regression models at a liberal P-value (P≤0.20) (Dohoo, Martin, & Stryhn, 2012).

Gestational age (weeks) at first ANC visits as a continuous variable was categorized into groups (<9 weeks and ≥9 weeks) for evaluation in the univariable analyses (Christianson et al., 2005, 2006; Finer & Zolna, 2014, 2016; Taye et al., 2018, 2019; Tinker et al., 2015). Additionally, parity as a continuous variable was categorized into two groups; =1=primiparous or >1=multiparous for assessment in the univariable analyses (Duong et al., 2012; Jawad et al., 2017). However, maternal age as a continuous variable was insignificant in the univariable analyses, thus, categorized into five groups and reassessed for statistical significance which was still insignificant. Nonetheless, the maternal age was further recategorized into two groups; <35 years, and ≥35, and reassessed for statistical significance. Women aged at least 35 years have previously been reported to have an increased likelihood of giving birth to children with MESBDs (Hollier et al., 2000). Paternal age as a continuous variable was similarly insignificant in the univariable analyses, thus categorized into seven groups and reassessed for statistical significance which was still insignificant. Nevertheless, paternal age was further recategorized into two groups (<35 years, and ≥35) and reassessed for statistical significance which was still insignificant. Males aged at least 35 years have previously been associated with an increased likelihood of defect-affected pregnancies/births in their female counterparts (Bray et al., 2006).

The variables found statistically significant in the univariable analyses were fitted to a multivariable model where a backward stepwise approach was used to eliminate variables from the model at P-value >0.05. The nature of pregnancy was however collinear in the multivariable analyses thus dropped in the final multivariable analysis. To minimize the confounding effects, elimination of non-significant predictors was only considered when their exclusion from the model did not yield more than a 30% change in the effects of the remaining variables (Dohoo et al., 2012). Two-way interactions were fitted between the remaining variables of the final model and assessed

for significance. A Hosmer-Lemeshow test was used to assess the goodness of fit of the logistic model, with a P-value of >0.05 being suggestive of a good fit.

The flow chart of the cases and controls recruited at study hospitals is shown in **Figure 6.**

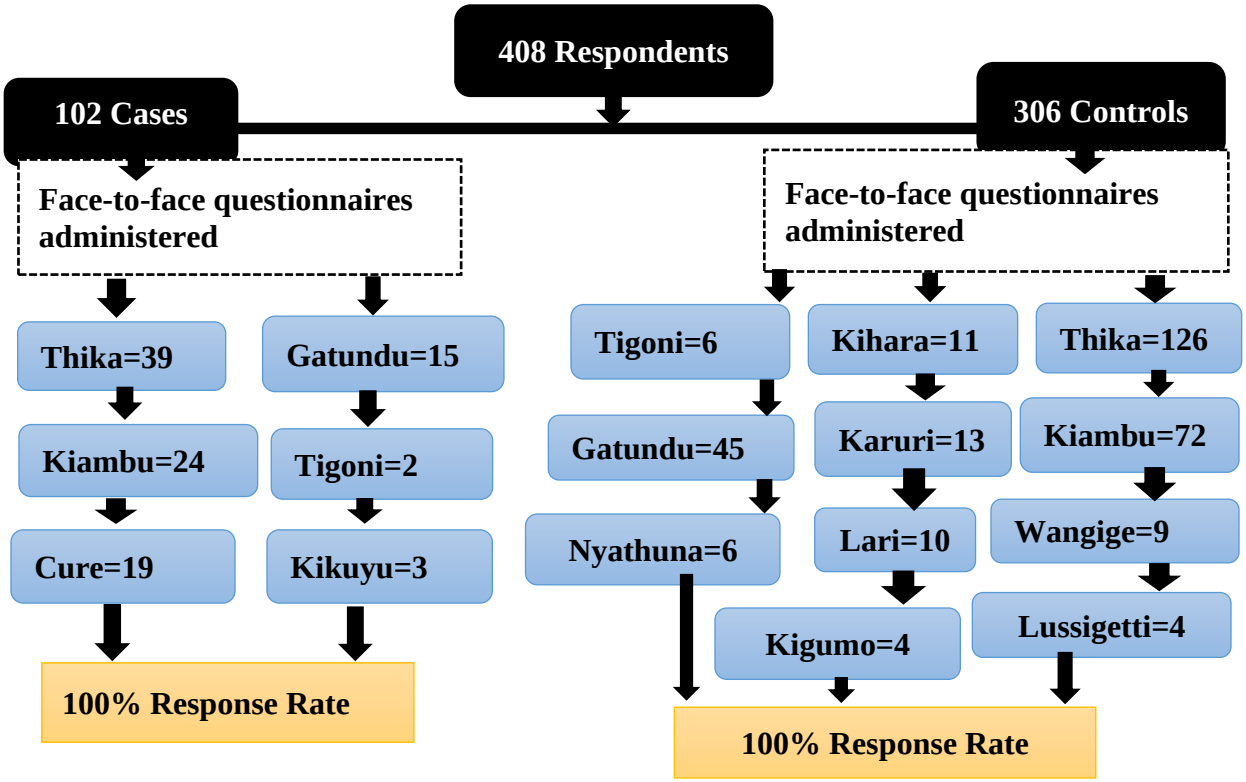


Figure 6: Flow chart of the cases and controls recruited at the study hospitals

4.3 Results

A total of 408 study respondents (102 cases and 306 controls) were enrolled in this study. The cases consisted of cleft lip with palate 1 (0.98%), cleft palate 3 (9.94%), clubbed hand 1 (0.98%), clubfoot 91 (89.22%), hydrocephalus 1 (0.98%), limb defects 4 (3.92%), and persistent cloacal 1 (0.98%).

4.3.1 Descriptive statistics

Sociodemographic-environmental factors: The median age of the study respondents was 26 years with a mean of 27.31 years (SD=5.73, R; 17-47) **(Table 5).** The median age of mothers in the case group was 28 years with a mean of 28.73 (SD=5.95, R; 19-47), whereas the median age of mothers in the control group was 26 years with a mean of 26.84 (SD=5.58, R; 17-42) **(Table 5).** The mean paternal age of the study respondents was 32.02 years with a standard deviation of 6.34 years and a median age of 31 years ranging between 19 and 56 years **(Table 5).** Of the 408

study participants, 184 (45.10%) had attained a secondary level of education; 38 (37.25%) and 146 (47.71%) in the case and control groups, respectively **(Table 5).**

Environmental teratogens: Of the 408 study respondents, 15 (3.68%) were exposed to farm-sprayed pesticides, of which 4 (3.92%) were in the case group and 11 (3.59%) were in the control group **(Table 5).**

Multifactorial inheritance: Of the 408 study respondents, 404 (98.77%) had single gestations for the "last-born" (current) children, of which 99 (97.06%) and 304 (99.35%) were in the case and control groups, respectively **(Table 5).** Of the study participants, 15 (3.68%) had given birth to children with birth defects in the previous gestations, with 9 (8.82%) in the case group and 6 (1.96%) in the control group. The median parity of the study respondents was 2 with a mean of 2.12 (SD=1.21, R; 1-8), whereas the median gestational age (weeks) at the first ANC visit of the study respondents was 20 weeks with a mean of 20.1 (SD=7,54, R; 4-40) **(Table 5).**

Table 5: Descriptive statistics for the study respondents (N=408)

Variables	**Measurements**	**Observations (N=408), n (%)**	**Cases (N=102), n (%)**	**Controls (N=306), n (%)**
Maternal residence	Thika	125 (30.64)	33 (32.35)	92 (30.07)
	Gatundu	62 (15.20)	13 (12.75)	49 (16.01)
	Kiambu	104 (25.49)	15 (14.71)	89 (29.08)
	Ruiru	38 (9.31)	20 (19.61)	18 (5.88)
	Others	79 (19.36)	21 (2.59)	58 (18.95)
Maternal age	<35	356 (87.25)	82 (80.39)	274 (89.54)
	≥35	52 (12.75)	20 (19.61)	32 (10.46)
Mean		27.31	28.73	26.84
Median		26	28	26
Standard deviation (SD)		5.73	5.95	5.58
Range (R)		17-47	19-47	17-42
Paternal age	<35	251 (67.11)	64 (70.33)	187 (66.08)
	≥35	123 (32.29)	27 (29.67)	96 (33.92)
Mean		32.02	31.3	32.25
Median		31	30	31
Standard deviation (SD)		6.34	5.47	6.59

Range		19-56	21-54	19-56
Maternal education	≤Primary	94 (23.04)	27 (26.47)	67 (21.90)
	Secondary	184 (45.10)	38 (37.25)	146 (47.71)
	Tertiary	130 (31.86)	37 (36.27)	93 (30.39)
Maternal occupation	Farming	24 (5.88)	7 (6.86)	17 (5.56)
	Unemployed	206 (50.49)	40 (39.22)	166 (54.25)
	Employed	178 (43.63)	55 (53.92)	123 (40.20)
Parity	Primiparous	127 (37.35)	28 (35.00)	99 (38.08)
	Multiparous	213 (62.65)	52 (65.00)	161 (61.92)
Mean		2.12	2.14	2.12
Median		2	2	2
Standard deviation (SD)		1.21	1.41	1.22
Range (R)		1-8	1-6	1-8
Nature of pregnancy	Multiple	5 (1.23)	3 (2.94)	2 (0.65)
	Single	403 (98.77)	99 (97.06)	304 (99.35)
Sex of the 'last-born' (current) child	Female	199 (48.77)	45 (44.12)	154 (50.33)
	Male	209 (51.23)	57 (55.88)	152 (49.67)
Siblings with a history of birth defects	No	393 (96.32)	93 (91.18)	300 (98.04)
	Yes	15 (3.68)	9 (8.82)	6 (1.96)
Gestational (age) weeks at first ANC visit	<9 weeks	23 (9.09)	9 (18.75)	14 (6.83)
	≥9 weeks	230 (90.91)	39 (81.25)	191 (93.17)
Mean		20.1	18.35	20.40
Median		20	18	21
Standard deviation (SD)		7.54	8.13	7.36
Range		4-40	4-35	4-40
Exposure to farm-sprayed pesticides	No	393 (96.32)	98 (96.08)	295 (96.41)
	Yes	15 (3.68)	4 (3.92)	11 (3.59)
Teratogenic therapeutic medicines for chronic illnesses	Medicines for hypertension	17 (4.17)	4 (3.92)	13 (4.25)
	No medicines for chronic illnesses	382 (93.63)	96 (94.12)	286 (93.46)

	Medicines for others chronic illnesses	9 (2.21)	2 (1.96)	7 (2.29)
Preconception folic acid intake	No	230 (56.65)	59 (57.84)	171 (56.25)
	Yes	176 (43.35)	43 (42.16)	133 (43.75)
ANC began eight weeks post-conception	No	330 (80.88)	77 (75.49)	253 (82.68)
	Yes	78 (19.12)	25 (24.51)	53 (17.32)

SD, standard deviation; R, range; ANC, Antenatal Care; Gatundu North and South sub-counties categorized as Gatundu sub-county, whereas Thika East and West sub-counties categorized as Thika sub-county.

Of the 15 study participants, 12 stated the name or described the nature of the defects in their previous pregnancies/births, however, 3 participants were unable to do so **(Table 5).** Of the 12 study respondents, 7 of the case subjects with congenital talipes equinovarus reported a history of birth defects in their previous births of which 4 subjects reported a recurrence of congenital talipes equinovarus, whereas 3 reported foot aversion, internally rotated shorthand (phocomelia), and congenital scoliosis **(Table 6)**. On the other hand, 5 control subjects reported a history of siblings with birth defects in their preceding births comprising 3 cases of congenital talipes equinovarus, 1 case of autism, and 1 case of deafness **(Table 6).**

Table 6: History of siblings with birth defects among case and control subjects

Types of MESBDs	Cases (n=102)	Controls (n=306)	Total (n=408)
Congenital talipes equinovarus	4	3	7
Autism		1	1
Deafness		1	1
Foot aversion	1		1
Internally rotated shorthand (phocomelia)	1		1
Congenital scoliosis	1		1
Total	**7**	**5**	**12**

MESBDs, Major External Structural Birth Defects

4.3.2 Logistic regression analyses

Notably, the factors assessed for statistical significance in the univariable analyses and found associated with MESBDs at a liberal P≤0.20 (Dohoo et al., 2012); included maternal age, residence, education, occupation, ANC visits beginning eight weeks post-conception, gestational age at first ANC visits, nature of pregnancy, and history of siblings with birth defects **(Table 7).** Subsequently, these variables were fitted to the multivariable model for the final analysis, except

education being distal relative to occupation, gestational age at first ANC visits, and ANC beginning eight weeks post-conception **(Figure 5).**

Table 7: Univariable analysis for the risk factors for MESBDs in Kiambu County, Kenya.

Variable	Value	Odds ratio	95% CI	P-value
Maternal residence*	Other sub-counties	Reference		
	Thika	0.99	0.52-1.86	
	Gatundu	0.73	0.33-1.61	<0.001
	Kiambu	0.47	0.22-0.98	
	Ruiru	3.07	1.37-6.89	
Maternal age*	<35	Reference		
	≥35	2.09	1.13-3.85	0.02
Paternal age	≥35	Reference		
	<35	1.22	0.73-2.03	0.45
Maternal education*	Tertiary	Reference		
	Secondary	0.65	0.39-1.10	0.18
	≤Primary	1.01	0.56-1.82	
Maternal occupation*	Farming	Reference		
	Employed	1.09	0.43-2.77	0.03
	Unemployed	0.59	0.23.1.51	
Preconception folic acid intake	No	Reference		
	Yes	0.94	0.60-1.47	0.78
ANC began eight weeks post gestation*	No	Reference		
	Yes	1.55	0.90-2.66	0.11
Gestational age at first ANC*	<9 weeks	Reference		
	≥9 weeks	0.32	0.13-0.79	0.01
Parity	Primiparous	Reference		
	Multiparous	1.14	0.68-1.93	0.62
Nature of pregnancy*	Multiple	Reference		
	Single	0.22	0.04-1.32	0.10
Sex of the 'last-born' (current) child	Female	Reference		
	Male	1.28	0.82-2.01	0.28
Siblings with a history of birth defects*	No	Reference		
	Yes	4.84	1.68-13.95	<0.01
Teratogenic therapeutic medicines for chronic illnesses	No medicines for chronic illnesses	Reference		
	Medicines for hypertension	0.92	0.29-2.88	1.0
	Medicines for other chronic illnesses	0.85	0.17-4.17	
Exposure to farm-sprayed pesticides	No	Reference		
	Yes	1.09	0.34-3.52	0.88

*Variables were eligible for inclusion in the multivariable model (P≤0.20); CI, Confidence Interval; MESBDs, Major External Structural Birth Defects.

In the multivariable analysis, only maternal residence at conception, and history of siblings with birth defects were shown as the significant predictors MESBDs at a 5% significance level **(Table 8).** Compared to women who conceived while residing in other sub-counties, women who conceived when residing in Ruiru were 5.28 times likely to give birth to children with MESBDs (aOR: 5.28; 95% CI: 1.68-16.58; P<0.01); whereas women who conceived when residing in Kiambu sub-county were 27% less likely give birth to children with MESBDs (aOR: 0.27; 95% CI; 0.076-0.95; P =0.04) holding all factors constant. Additionally, compared to siblings without a history of birth defects, siblings with a history of birth defects were 7.65 times likely to be born with MESBDs (aOR: 7.65; 95% CI; 1.46-40.01; P =0.02) holding all factors constant (**Table 8).**

Table 8: Multivariable analysis for the risk factors for MESBDs in Kiambu County, Kenya.

Variable	Value	aOR	95% CI	P-value
Maternal residence at conception*	Other sub-counties	Reference		
	Kiambu*	0.27	0.076-0.95	0.04
	Ruiru*	5.28	1.68-16.58	<0.01
	Thika	0.77	0.29-2.03	0.59
	Gatundu	0.96	0.33-2.88	0.96
Siblings with a history of birth defects*	No	Reference		
	Yes	7.65	1.46-40.01	0.02
Maternal age	<35	Reference		
	≥35	0.80	0.26-2.49	0.70
Maternal occupation	Farming	Reference		
	Employed	0.81	0.18-3.74	0.80
	Unemployed	0.83	0.18-3.78	0.81
ANC began eight weeks post gestation	No	Reference		
	Yes	1.07	0.07-16.31	0.96
Gestational age (weeks) at first ANC visit	<9 weeks	Reference		
	≥9 weeks	0.27	0.02-4.09	0.34

*Variables that were statistically significant at 5% significance level; aOR, Adjusted Odds Ratio; CI, confidence interval; MESBDs, Major external Structural Birth Defects

4.4 Discussions

To my knowledge, this was the first case-control study conducted to identify the risk factors for MESBDs in the entire county. The study results mimicked other research findings across the world that maternal residence at conception and history of siblings with birth defects are strongly associated with the intrauterine formation of MESBDs (Christianson et al., 2005, 2006; Romitti, 2007). The study observed orofacial clefts comprising 1 (0.98%) cleft lip with the palate, and 3 (9.94%) cleft palates; limb reduction defects comprising 1 (0.98%) clubbed hand, and 4 (3.92%)

limb defects; defects of the musculoskeletal system consisting of 91 (89.22%) clubfeet; and neural tube defects comprising 1 (0.98%) hydrocephalus and 1 (0.98%) persistent cloacal. These are some types of defects associated with genetic, partially genetic, and multifactorial etiology (Christianson et al., 2005, 2006; Romitti, 2007). The prevalence of such defects has been observed to vary by region attributed to ethnic and socioeconomic differences globally (Christianson et al., 2005, 2006).

Siblings with a positive history of MESBDs among their preceding siblings are at most risks of being born with MESBDs, have a recurrence of similar defects among the siblings, and/or among their offspring (Romitti, 2007). This was evident in this study where 4 of the case subjects with clubfoot similarly reported clubfoot in the preceding siblings, whereas 3 of the case subjects with clubfoot reported foot aversion, internally rotated shorthand (phocomelia), and congenital scoliosis each in the preceding siblings. This study similarly made remarkable observations where case subjects with clubfoot reported concurrence of congenital pes planus, and arthrogryposis each, whereas a case subject with hydrocephalus reported concurrence of congenital pes planus, and two case subjects of limb defects each reported concurrence with Down syndrome. On the other hand, 5 control subjects reported a history of siblings with birth defects in the preceding births comprising 3 cases of clubfoot, 1 case of autism, and 1case of deafness. Positive siblings and familial history of specific types of MESBDs have been associated with increased risks of recurrence in subsequent pregnancies (El Koumi et al., 2013; Mashuda et al., 2014; Romitti, 2007). The recurrence rate of NTD and Down syndrome have been approximated at 2-5% and 1% respectively (El Koumi et al., 2013; Mashuda et al., 2014; Romitti, 2007), whereas recurrence of orofacial clefts particularly cleft lip with a cleft palate could be as high as 25% for cases with no familial history of birth defects but have an underlying genetic etiology (Romitti, 2007). Thus accurate knowledge of birth defects by families when given to the clinicians is similarly of public health significance to improve risk assessments and reproductive health planning for couples susceptible to birth defects of genetic and multifactorial origin (Romitti, 2007).

Even though this study did not show a significant statistical association between MESBDs with parental age, advanced age beyond 35 years has been strongly associated with defects of chromosomal etiology such as Down syndrome, and those of non-syndromic etiology including

neural tube defects and orofacial clefts (Bray et al., 2006; Christianson et al., 2005, 2006; Gill et al., 2012). Nonetheless, this study alluded to an increased risk of chromosomal abnormalities, thus suggestive of the prevalence of MESBDs of genetic origin in the county. High prevalence of Down syndrome has been observed in developing countries attributed to many older women becoming pregnant, limited family planning services, unavailability of prenatal genetic counselling, screening, diagnosis, and related services (Christianson et al., 2005, 2006). MESBDs are considered defects of public health importance, however, the presence of certain defects; rare or common, minor or major, internal or external, functional or structural sometimes act as pointers to latent defects of similar significance because of the multiple genetic epidemiology, thus could be diagnosed later using advanced medical imaging techniques (Parker et al., 2010; Romitti, 2007; Sever, 2004).

The study similarly observed maternal residence at conception as a predictor of the intrauterine formation of MESBDs. The study showed that women who got pregnant when residing in Ruiru sub-county were 5.28 times likely to give birth to children with MESBDs compared to those who got pregnant residing in other sub-counties within Kiambu County. Conversely, the study showed that women who got pregnant when residing in Kiambu sub-county were 27% less likely to give birth to children with MESBDs compared to those who got pregnant residing in other sub-counties within the county. Thus, this study showed that Kiambu sub-county was protective implying it was relatively safe for women of reproductive age to become pregnant while residing in the sub-county. Maternal residence at the time of conception as a risk factor for MESBDs could be ascribed to variations in genetic, multifactorial, sociodemographic-environmental attributes among women of reproductive age. From the genetic perspective, increased frequency of single-gene defects in developing countries has been associated with increased frequency of common recessive disorders such as haemoglobin disorders, sickle cell anaemia, thalassemia, oculocutaneous albinism, and cystic fibrosis because of the discerning advantage for carriers to the mortal effects of malaria, as well as recessive conditions associated with high rates of consanguineous (cousin) marriages (Christianson et al., 2005, 2006).

High prevalence of defects of chromosomal etiology in developing countries has also been ascribed to women delaying childbearing beyond 35 years, limited maternal access to family

planning services, and absence of clinical genetic services (Christianson et al., 2005, 2006; Gill et al., 2012; Mashuda et al., 2014). Sociodemographic-environmental characteristics and physiological interactions between complex genetic disorders and idiopathic environmental factors could also lead to the occurrence of MESBDs associated with ethnic and geographical differences (Christianson et al., 2005, 2006). Thus, the epidemiology of MESBDs in the county underscores an underlying genetic, multifactorial, and sociodemographic-environmental etiology contributing to the global debate on the burden of a "silent" public health problem in the developing countries (Christianson et al., 2005, 2006).

Although this study did not show an association between MESBDs with known environmental factors (teratogens and micronutrient deficiencies), pregnancies in developing countries are at increased risk of potential teratogens because of the high prevalence of intrauterine infections, maternal malnutrition, low socioeconomic levels, low levels of education, deficient environmental protection policies, and insufficiently regulated access to medicines (Christianson et al., 2005, 2006). This could imply the county is performing relatively well in controlling potential environmental causes of MESBDs. The teratogens consist of; (i) congenital infections; (ii) maternal and altered metabolism; and (iii) recreational and therapeutic drugs (Christianson et al., 2005, 2006). Congenital infections comprise toxoplasmosis, other infections (syphilis, varicella-zoster, human parvovirus B19), rubella, cytomegalovirus, and herpes, denoted by an acronym "TORCH" (Christianson et al., 2005, 2006). Epilepsy and insulin-dependent diabetes are examples of maternal illnesses and altered metabolism, whereas statins and alcohol are examples of therapeutic and recreational drugs, respectively (Christianson et al., 2005, 2006). This study also did not show significant associations between MESBDs with maternal occupation, gestational age at first ANC, and ANC beginning eight weeks post-conception; factors thought to influence maternal iron-folic acid supplementation (Grossman, 1972; Kabubo-Mariara et al., 2012; Wagstaff, 1986). Folic acid is crucial for the biosynthesis, and methylation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) which are important for cell division, differentiation, and regulation of gene expression, during rapid cell division during such as embryogenesis, thus is necessary for the growth and smooth functions of human cells (Florentina Mashuda, 2014; WIŚNIEWSKA & Wysocki, 2008).

Nevertheless, some limitations were inherent in this study; there was a likelihood of differential recall bias among the study respondents; cases were more likely to remember their preconception period owing to the experience of MESBDs in the last birth than the controls, thus bias could affect estimates of the odds ratios. The study participants with a history of siblings with birth defects either stated or described the nature of the defects however the researchers could not ascertain the accuracy of the diagnoses/descriptions, while others did not know the names of the defects. Survivor bias was also an inherent limitation in this study because some defects such as neural tube defects are potentially fatal, however, the study could not establish the cause of deaths among stillbirths, and miscarriages in the study hospitals because it was not a pathological standard operating procedure in the entire country. Additionally, due to the extreme rarity of MESBDs because of the absence of public health surveillance systems, the researchers lumped all types of MESBDs in calculating the sample size, yet births defects are largely heterogenous in their etiology, thus could lead to underestimation of the effects of the predictors on the odds of MESBDs.

4.5 Conclusions and recommendations

These findings were suggestive of genetic, multifactorial, and sociodemographic-environmental etiology of MESBDs in Kiambu County. These findings could provide the greatest public health opportunities for health planners in the region to establish defect-specific surveillance programs, implement proven public health preventive strategies, and provide appropriate treatment interventions for the most prevalent MESBDs. Therefore, I would like to provide the following policy recommendations; establishment of hospital-based surveillance systems for the most common MESBDs, and integration of clinical genetic services with routine reproductive health services, nationally. The genetic services should consist of counselling, screening, diagnosis, and associated treatment including elective termination of pregnancies for anomalies in jurisdictions with favourable legislative frameworks. Additionally, I would recommend further epidemiological and economic evaluation studies to understand the epidemiology and economic burden of these defects in Kenya.

CHAPTER FIVE: COST ANALYSIS OF OUTPATIENT SERVICES FOR MAJOR EXTERNAL STRUCTURAL BIRTH DEFECTS: AN INGREDIENT APPROACH IN SELECTED HOSPITALS IN KIAMBU COUNTY, KENYA

Abstract

Background: Major external structural birth defects are known to exert an enormous economic burden on individuals and health services; however, they have been vastly unappreciated and underprioritized as a public health problem in settings where cost analyses are limited.

Objective: The objective of this study was to conduct a cost analysis of outpatient services for major external structural birth defects in four selected hospitals within Kiambu County, Kenya.

Methods: A hospital-based cross-sectional study design was adopted in four hospitals where ingredient approaches were used to retrospectively gather data on cost drivers for interventions comprising castings, bracings, tenotomies, physical and developmental therapies from health care providers' perspectives for a one-year time horizon from January 1st, 2018, to December 31st, 2018. The hospitals were purposively and randomly selected for providing outpatient corrective and rehabilitative services to the under-fives where prevalence-based morbidity data were extracted from the outpatient occupational therapy clinic registers to generate data on direct cost drivers. On the other hand, the staff-time for the hospitals' executives comprising the medical superintendents, chief nursing officers, orthopaedic surgeons, and health administrative officers were gathered through face-to-face enquires from the occupational therapists being the closest proxies for the officers to generate data on indirect cost drivers. Following a predefined inclusion criterion, 349 cases were determined whose associated cost drivers measured using review of outpatient registers, face-to-face inquiries, and activity-based costing techniques were valued using prevailing market prices. The costs were categorized as recurrent only because capital costs did not suffice in this study. The costs were then assigned to direct, and indirect cost centers using the step-down cost accounting technique for computation of the total costs at the final cost center. Intermediate costs were however not identified in this study thus were excluded from the analysis. The costs allocated to the direct cost center consisted of the intervention costs for the defects, staff salaries, and benefits, whereas the costs assigned to the indirect cost center comprised building space, utility charges, and administrative staff-time. Subsequently, the unit economic cost of outpatient services for all the defects was calculated based on average costs by dividing the final total costs by the number of cases (caseload) and expressed in U.S Dollars. Overhead costs which consisted of staff emoluments, building space, administrative staff-time, and utility charges were

proportionally allocated to the individual defects in addition to the costs of specific interventions for calculation of the total costs of individual defects. Similarly, the unit economic cost of outpatient services for every defect was calculated based on average costs by dividing the total costs by the number of cases (caseload) for every defect and expressed in U.S Dollars. However, the costs were not discounted for differential timing because capital costs were not considered in the estimation of the economic costs whereas the inputs were measured for a one-year time horizon. Finally, the costs were inflated using the consumer price index (CPI) to minimize uncertainties ascribed to the scantiness of cost data, methods of gathering data for cost analysis, and changes in pricing health resources between January 2018 to December 2018.

Results: The unit economic cost of all the cases (caseload) was estimated at $ 1,139.73; and $ 1,143.51 for neural tube defects, $ 1,143.05 for congenital talipes equinovarus, and $ 1,109.81 for congenital pes planus. Salaries and benefits of the occupational therapist were the major cost drivers for the outpatient services accounting for more than 70% of the total costs of major external structural birth defects in the county.

Conclusion: The highest economic burden of major external structural birth defects in the county was associated with neural tube defects followed by congenital pes planus despite having the fewest caseloads, respectively. Thus, I would like to recommend efficiency in resource allocation for occupational and rehabilitative health services to minimize expenditures on staff salaries and benefits in Kiambu County, Kenya.

Keywords: Major external structural birth defects, costing analysis, outpatient services, an ingredient approach, step-down cost accounting, county, Kenya

5.1 Introduction

Major external structural birth defects (MESBDs) are defined as physical abnormalities of intrauterine origin present from birth, detectable visually, and have significant health and development impacts (Christianson et al., 2005, 2006; WHO, 2014, 2020). These defects are potentially fatal, and children who survive beyond infancy require substantial economic resources to deal with lifelong disabilities (Andegiorgish et al., 2020; Bhide & Kar, 2018; Feldkamp et al., 2017; Tinker et al., 2015; Waitzman et al., 1994). Worldwide, approximately 134 million births occur annually of which 7.9 million (6%) are born with at least a major birth defect, mostly affecting the central and musculoskeletal systems (Christianson et al., 2005, 2006; WHO, 2013, 2014, 2020). Although about 3.3 million of these children die before they are five years old, the 3.2 million who survive may be disabled for life if sufficient resources are not dedicated to corrective and rehabilitative health services (Bhide & Kar, 2018; Christianson et al., 2005, 2006).

MESBDs continue to occur attributed to the genetic, environmental, and multifactorial factors thus exerting an enormous economic burden on individuals and health services, however, they have been vastly ignored and unappreciated as a public health problem in the region (George N Agot, Mweu, & Wang'ombe, 2021; George Nyadimo Agot et al., 2020; Bowles et al., 2014; Christianson et al., 2005, 2006; Waitzman et al., 1994). Even though these defects remain a “silent” global public health problem, the highest-burden is shouldered by populations in developing counties due to the prevalence of the risk factors coupled with a lack of knowledge on the main cost drivers attributed to the scantiness of and inaccurately profiled cost drivers as well as inadequate expertise in economic evaluation studies (Bhide et al., 2016; Bhide & Kar, 2018; Christianson et al., 2005, 2006; Feldkamp et al., 2017; Feldkamp et al., 2015; Parker et al., 2010; Waitzman et al., 1994; WHO, 2014, 2020; Wu et al., 2013). Hospital charges for new-born children with some forms of birth defects have been reported as four to eight times higher than those without any form of birth defects (Simeone et al., 2015). Cost analysis is a partial economic method of evaluating health care programs used to compare the costs of at least two alternative interventions; however cost analysis studies are still useful even in the absence of comparative interventions as they can be used to establish baseline economic costs of health interventions (Drummond et al., 2015; Kirigia, 2009; Mugisha et al., 2002).

Children surviving beyond infancy could require restorative health services to reduce the adverse impacts associated with MESBDs (Christianson et al., 2005, 2006). These interventions are described as corrective and rehabilitative outpatient services consisting of castings, bracings, tenotomies, physical and developmental therapies whose monetary value is referred to as economic or opportunity costs (Conteh & Walker, 2004; Cunningham, 2000; Drummond et al., 2015; Kirigia, 2009; McIntosh, 2006; Sandmann et al., 2018; Walker & Kumaranayake, 2002). The resources used in the provision of such services could be quantified through micro-costing (bottom-up) using an ingredient approaches to gather data on the costs drivers by a step-down full costing technique, activity-based costing, time and motion, surveys, and manager interview techniques (Conteh & Walker, 2004; Drummond et al., 2015; Husereau et al., 2013; Kirigia, 2009; Mogyorosy & Smith, 2005). Alternatively, these inputs may be quantified by gross costing (top-down) using historical outlay of resources (Conteh & Walker, 2004; Drummond et al., 2015; Husereau et al., 2013; Kirigia, 2009; Mogyorosy & Smith, 2005).

The range, contexts, and extents of cost elements are determined by economic viewpoints consisting of health care providers', individuals', or societal perspectives that are informed by policy decisions to determine the study objectives, and questions (Conteh & Walker, 2004; Drummond et al., 2015; Husereau et al., 2013; Kirigia, 2009; Mogyorosy & Smith, 2005). The existing market prices and opportunity costs (forgone benefits) are used to value the inputs in the monetary units categorized as recurrent and capital costs (Conteh & Walker, 2004; Cunningham, 2000; Drummond et al., 2015; Kirigia, 2009; McIntosh, 2006; Sandmann et al., 2018; Walker & Kumaranayake, 2002). These costs are assigned to direct, indirect, and intermediate cost centres using a step-down accounting technique (Conteh & Walker, 2004; Cunningham, 2000; Drummond et al., 2015; Kirigia, 2009; McIntosh, 2006; Sandmann et al., 2018; Walker & Kumaranayake, 2002). The costs of the inputs are sometimes shared among the cost centres thus referred to as overhead (shared or joint) costs which are proportionally allocated to the respective cost centres for estimating final economic costs (Drummond et al., 2015; Kirigia, 2009). Capital costs determined for more than a one-year time horizon should be considered for the differential-time discounting unlike the recurrent costs (Conteh & Walker, 2004; Cunningham, 2000; Drummond et al., 2015; Kirigia, 2009; McIntosh, 2006; Sandmann et al., 2018; Walker & Kumaranayake, 2002). Similarly, statistical and/or sensitivity analysis should be conducted to ascertain the

robustness of the evaluation findings because of potential uncertainties arising from sample size determination and data collection methods for the cost drivers (Drummond et al., 2015).

Worldwide, the advancements in medical and surgical interventions are known to reduce the severity of lifelong physical disabilities associated with MESBDs; however, their costs are catastrophic and prohibitive to many households and public health care systems (Christianson et al., 2005, 2006; Waitzman et al., 1994; Wu et al., 2013). Even though substantial resources are usually allocated to health care systems for the provision of corrective and rehabilitative health services for MESBDs, their costs are seldom estimated especially in developing countries due to the rarity and stochasticity of the defects, scantiness of the cost data, inaccurately profiled cost information, and inadequate costing expertise (Conteh & Walker, 2004; Gedefaw et al., 2018; Khurmi et al., 2014; Mugisha et al., 2002). The scarcity of local epidemiological data and differences in the epidemiological study designs (prevalence/incidence-based) also impede the accuracy of profiled cost data in developing countries (Conteh & Walker, 2004; Gedefaw et al., 2018; Khurmi et al., 2014; Mugisha et al., 2002).

Economic costs increase the extent to which health services, individuals, and society are affected by MESBDs because of the forgone benefits of not investing in the next best alternative (Conteh & Walker, 2004; Cunningham, 2000; Drummond et al., 2015; Kirigia, 2009; McIntosh, 2006; Preedy & Watson, 2010; Sandmann et al., 2018; Simeone et al., 2015; Walker & Kumaranayake, 2002). Corrective and rehabilitative health care services for MESBDs are critical in reducing the severity of lifelong disabilities and improving the quality of life for the affected children, as well as the economic productivity of the affected families (Christianson et al., 2005, 2006; Waitzman et al., 1994). Thus, cost analysis is of public health importance in influencing and informing health planning, policy decisions, resource allocations, informing further economic evaluations, and assessing health system performance (Birch & Gafni, 1996; Briggs et al., 1994; Conteh & Walker, 2004; Cunningham, 2000; Drummond et al., 2015; Kirigia, 2009; Sandmann et al., 2018). Consequently, the objective of this study was to conduct a cost analysis of the outpatient services for MESBDs from the providers' viewpoints using an ingredient approach in selected hospitals in Kiambu County, Kenya.

5.2 Methods

5.2.1 Study settings, and designs

The study was conducted in four hospitals consisting of three county referral hospitals (Kiambu, Thika, and Gatundu), and PCEA Kikuyu orthopaedic (faith-based) selected for providing corrective and rehabilitative outpatient health services to children born with MESBDs in the county. The three-county referral hospitals were purposively selected being the only public hospitals providing these services in the county, whereas PCEA Kikuyu orthopaedic hospital (faith-based) was selected by a simple random sampling technique using sealed envelopes between two faith-based hospitals for providing the same services in the county. A hospital-based cross-sectional study design was adopted to generate cost data from prevalence-based local morbidity data gathered retrospectively using ingredient approaches to estimate the economic costs of corrective and rehabilitative outpatient health services from health care providers' perspectives. This was however the best choice of the study design for measuring the unit economic cost of health services as an attribute of the population, and thus provided a snapshot of the burden associated with the 'silent' public health problem and allowed for generalization of the study results in similar hospital settings in the region. Even though incidence data were readily available and easily accessible for the costing activity, prevalence-based data were extremely preferred to improve the accuracy of the profiled cost data and the estimation of the unit economic costs. This was an economic evaluation study, therefore was reported as per the CHEERS (checklist for consolidated health economic evaluation reporting standards) guidelines (Husereau et al., 2013).

5.2.2 Study population and eligibility for participation

The study population consisted of all children aged under five years old born to resident women of Kiambu County between January 1st, 2014, and December 31st, 2018. Cases were defined as live births with at least one clinically obvious major external structural birth defect referenced/or described by assistant occupational therapists and/or orthopaedic surgeons and presented to the occupational therapy clinics for care from January 1st, 2018, to December 31st, 2018. Caregivers of children born with MESBDs were likely to seek outpatient corrective and rehabilitative health services at the study hospitals whether the children were born in health facilities, communities, and in or out of the county. Thus, the eligibility criterion defined above could minimize systemic bias and ensure the reliability of the study results.

5.2.3 Study perspective, time horizon, and unit cost estimations

The data for cost drivers were gathered retrospectively from health care providers' perspective for a one-year time horizon between January 1st, 2018, and December 31st, 2018, for purposes of maintaining similar currency conversion. The total (annual) economic costs were calculated for the defects (349 cases) for computing the unit economic costs as an average of the total costs expressed in Kenya Shillings (KES). The unit economic costs were calculated by dividing by the total annual costs by the number of cases using the following formula ***(Equation 7):*** -

$$\textbf{Unit economic costs } (\$) = \frac{\textbf{Total economic costs } (\textbf{KES})}{\textbf{Total number of cases}} \qquad \boldsymbol{Equation}\ (\mathbf{7})$$

5.2.4 Currency conversion

Further, the unit economic costs were converted to United States Dollars ($) at an existing currency exchange rate of KES 98.00 equivalent to $1.00 in December 2018 using the following formula ***(Equation 8):*** -

$$\textbf{Unit economic costs } (\$) = \frac{\textbf{Total economic costs } (\textbf{KES})}{\textbf{KES 98.00}} \qquad \boldsymbol{Equation}\ (\mathbf{8})$$

5.2.5 Assumptions

The study assumed that the existing currency exchange rate of KES 98.00 in 2018 reflected the global Purchasing Power Parity (PPP) and inflation factor.

5.2.6 Discounting for differential timing

The costs were not discounted for the differential timing because capital costs did not suffice, whereas only a one-year time horizon was considered in this study.

5.2.7 Data collection process

Before data collection, the Principal Investigator (PI) recruited and trained four nursing graduates as Research Assistants (RAs) to ensure that the data abstraction process spanned for two months from August 1st, 2019, to September 30th, 2019, was carried out in a standardized manner. The study adopted ingredient approaches including review of outpatient registers, activity-based costing techniques, and face-to-face inquiries to gather data for cost analysis of outpatient services

for MESBS in the county. The prevalence-based morbidity (caseload) data were gathered using an activity-based costing technique by retrospectively reviewing the outpatient occupational therapist registers where 349 cases were determined following a predefined inclusion criterion and entered in predetermined secondary data abstraction tools for valuation using prevailing market prices. These registers contain information on health services provided to children with major external structural birth defects including dates of clinic visits, outpatient numbers, names of the patients, patients' age, residence, diagnoses, and therapeutic interventions, among others.

On the other hand, the cost drivers for bracings, tenotomies, castings, physical and developmental therapies were retrospectively gathered using activity-based costing techniques, entered in predefined secondary data abstraction tools, and valued using prevailing market prices. The ingredients for the above-mentioned interventions included (i) the number of bracings, the first and review visits for bracings, (ii) quantity of casting materials, (iii) the number of castings, first and review visits for castings, (iv) the number of tenotomies, first and review visits for tenotomies, and (v) emoluments for occupational therapists, and support staff. The value of physical and developmental therapies was accounted for by the number of review visits for bracings, castings, and tenotomies aimed at achieving full functionality of the affected children.

Additionally, staff-time for the hospitals' executives comprising the medical superintendents, chief nursing officers, orthopaedic surgeons, and health administrative officers were gathered through face-to-face inquiries from the occupational therapists being the closest proxies for the officers mentioned above. The staff-time was valued using prevailing market prices and entered in predefined secondary data abstraction tools. Finally, building space for renting, and utility charges for water and electricity were gathered using activity-based costing techniques, valued using market prices, and entered in predefined secondary data abstraction tools. The ingredient techniques and prevalence-based data were chosen for the possibility of generating detailed and accurately profiled cost data. The data for the cost drivers of the interventions gathered comprised the following: -

Prevalence-based caseloads/morbidity data: The sampling strategy for the cost analysis study is illustrated in the diagram below **(Figure 7).**

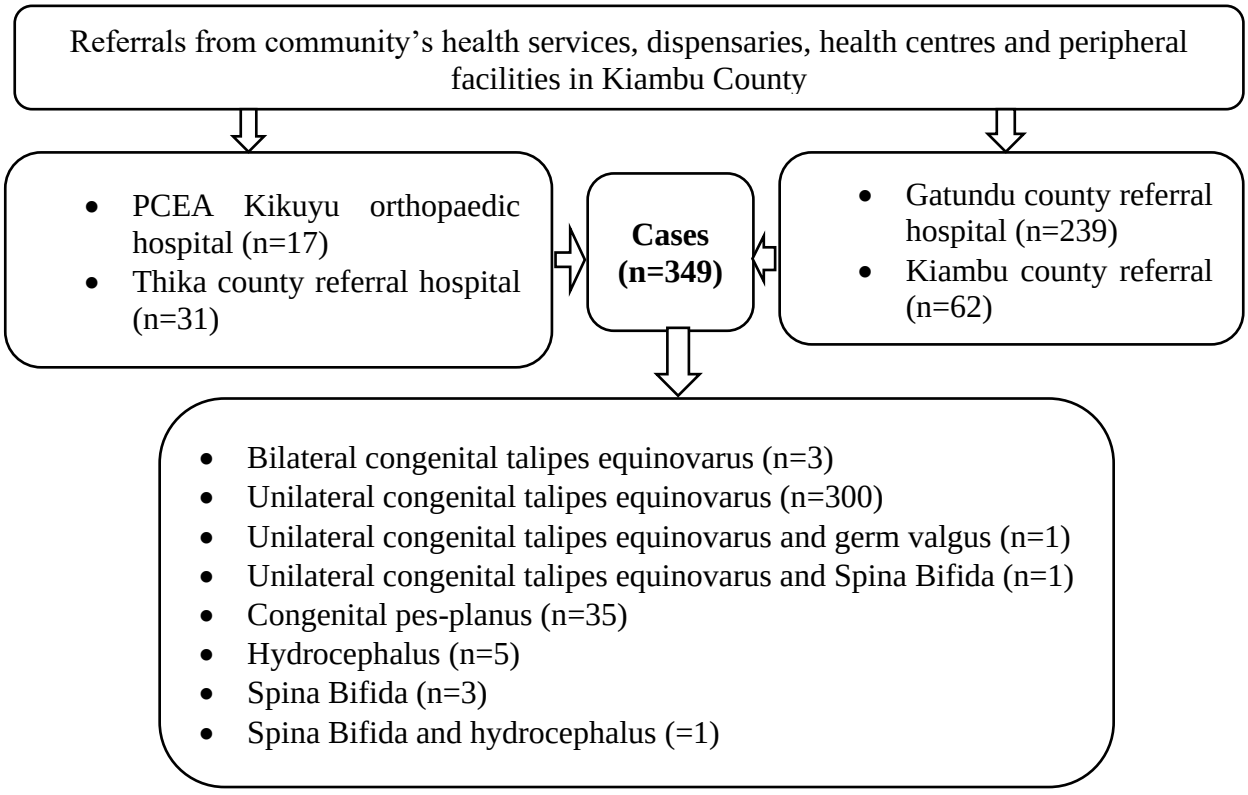


Figure 7: Flow chart for costing study

Castings: Castings are used as outpatient interventions for stabilizing and repositioning foot structures of the affected children. The materials for casting consisting of Plaster of Paris (POP) bandages, orthopaedic cotton bandages, and glycerine were measured and valued at $ 3.9 using prevailing local market prices. A set of these materials were used to cast two cases of clubfoot; thus, the study computed the number of castings and the number of visits after the procedure for all cases of CTEV and congenital pes planus treated using this strategy.

Bracings: Bracings are also used as outpatient interventions for stabilizing and repositioning foot structures made of leather foot covers, rubber soles, and metallic rods used to stabilize cases of clubfoot. Braces were sourced from the local markets as ready-made products, therefore, were valued at $ 15.31 using prevailing market prices. The study also enumerated the number of braces and the number of visits after the procedure for all cases of CTEV treated using this strategy.

Tenotomies: Tenotomy is a procedure performed by surgeons to extend the Achilles tendon in cases of clubfoot. This is largely an outpatient specialized procedure, therefore existing market hospital charges for outpatient specialized surgical procedures were used to value the cost of

tenotomies at $ 51.02. Similarly, the number of tenotomies and the number of visits after the procedure were computed for all the cases of CTEV where this treatment strategy was adopted.

Physical and developmental therapies: These interventions are aimed at optimizing the functionality of the children with MESBDS thus were quantified as the number of secondary visits following corrective and rehabilitative interventions consisting of castings, bracings, and tenotomies and valued using prevailing market rates.

Emolument for personnel: The personnel comprised of assistant occupational therapists and support staff whose emolument was estimated based on the respective schemes of service for staff with at least ten years of work experience in government (GoK, 2014; SRC, 2014, 2015). Emoluments for assistant occupational therapists consisted of basic salary, house allowance, commuter allowance, health risk allowance, and health extraneous allowance, whereas, for the support staff comprised basic salary, house allowance, and commuter allowance (GoK, 2014; SRC, 2014, 2015). The monthly salary and benefits for an assistant occupational therapist at "Grade 10'' were valued at $ 1,224.50, whereas support staff at "Grade 14'' was valued at $ 173.50.

Renting building space: Occupational therapy outpatient clinics were identified within the respective study hospitals whose plinth floor surface areas were measured in square feet and valued based on the existing local market rates for renting building spaces. The total renting space for the four hospitals was estimated at 3,593.63 square feet and valued at $ 0.37 per square feet local market value.

Utility charges: Utilities included electricity; and water and sewerage estimated at $ 25.51 and $ 30.61 per month, respectively.

Administrative staff-time: The staff-time for the medical superintends/directors, orthopaedic surgeons, chief nursing officers/directors, and health administrative officers/directors were identified and measured by consensus through face-to-face inquiries made to the assistant occupational therapists being the closest proxies for the above-mentioned officers. The staff-time for medical directors and orthopaedic surgeons was measured as a single specialized medical practitioner's consultation valued at $ 20.40 and quantified for five days a week for one calendar year. The staff-time for nursing directors and administrative directors on the other hand was

measured as a single general medical practitioner's consultation valued at $ 10.20 for five days a week for one calendar year.

5.2.8 Ethical approvals, authorizations, and considerations

Ethical approval was obtained from Kenyatta National Hospital (KNH)-University of Nairobi (UoN) Ethics Review Committee (Ref. No: KNH-ERC/A/44). The National Commission for Science, Technology, and Innovation further granted us permission vide a letter Ref. No: NACOSTI/P/19/75586/28325 to collect data in Kiambu County. The County Commissioner of Kiambu also provided an authorization Ref. No: ED.12 (A)/1/VOL.11/107 and copied to the County Director of Education who acknowledged by stamping the letter. The County Director of Health, Kiambu County similarly authorized this study to vide a letter Ref. No: KIAMBU/HRDU/AUTHO/2019/03/06/AgotGN. The study was conducted in 4 hospitals (three county referral hospitals, and a faith-based hospital) that granted additional permissions through written authorizations or counter approving the authorization letter issued by the County Health Directorate. The Medical Superintend of Thika county referral hospital authorized the study to vide a letter Ref. No. MOMS/TKA/VOL.III (728), whereas Gatundu county referral hospital issued an authority vide a letter Ref: GTD/GEN/37/VOL.1/97. The Medical Director of PCEA Kikuyu hospital granted permission after a written commitment by the Principal Investigator (PI) to submit the report of the study upon completion. The data collected were de-identified using anonymous codes and entered in a laptop secured by an alphanumeric coded key only known to the PI to maintain confidentiality. Patients were not directly involved in this study because data was gathered from the medical registers, thus consent was not required.

5.2.9 Minimization of biases

Case ascertainment, information, and systemic biases were expected in this study; therefore, the PI began by predefining an eligibility criterion (case definition) for participation in the study and predetermining a secondary data abstraction tool for purposes of reducing case ascertainment biases. On the other hand, information biases were reduced by training the data collectors on secondary data extraction techniques from the outpatient occupational therapy clinics and entering data into the abstraction tools to ensure the process was conducted in a standardized manner. Further, all the registers for the entire one-year study period (2018) were reviewed and listed all the cases of major external structural birth defects to reduce ascertainment and information biases

in this study. Systemic bias was also reduced by excluding cases of delayed milestones, and/or developmental conditions due to management intervention similarities.

5.2.10 Statistical analysis

Following data collection, filled secondary data abstraction tools were manually checked daily for accuracy and completeness and subsequently entered in a Microsoft Excel spreadsheet (Microsoft Office Professional Plus 2019) by two independent data managers to reduce potential errors. The PI cross-checked and validated the computerized dataset against predetermined data abstraction tools for analyses. Descriptive qualitative categorical variables were summarized in frequency tables, proportions, and percentages to show their distributions, whereas continuous variables were summarised and presented in means (averages). The final product was defined, costs categorized as recurrent and allocated to direct and indirect cost centers using step-down cost accounting technique for calculation of the total costs at the final cost centres as follows: -

The final product: This was defined as the economic cost of outpatient services for MESBDs among under-fives computed as total economic and unit economic costs of the individual and collective MESBDs.

Direct cost center: The costs assigned to the direct cost center consisted of; (i) prevalence-based morbidity data, (ii) the number of bracings, the number of bracing first visits and review visits, (iii) the number of castings, the number of casting first visits and revisits, (iv) the number of tenotomies, the number of tenotomies first visits and revisits, (v) the number of occupational therapists and their emoluments, and (vi) the number of support staff and their emoluments. Notably, the number of clinic revisits accounted for the value of resources invested in physical and developmental therapies following castings, bracings, and tenotomies.

Indirect cost center: Additionally, the costs assigned to indirect cost center comprised; (i) the number of orthopaedic surgeons and associated staff-time, (ii) the number of medical superintendents/directors, and associated staff-time, (iii) the number of chief nursing officers/directors and associated staff-time, (iv) the number of health administrative officers/directors and associated staff-time, (v) building space for rental, and (vi) utility charges.

Final cost center: The costs allocated to the direct and indirect cost centers constituted the costs allocated to the final cost center using a step-down cost accounting technique for the computation of the total economic costs. However, capital costs did not suffice in this cost analysis study

because movable, and fixed capital resources were not considered for valuation due to non-existing inventory records for furniture, examination couches, and capital donations in kind, nonetheless these resources appeared to have been lost more than half of their economic half-lives. Additionally, motor vehicles, motorcycles, and bicycles were not used either as direct, indirect, or intermediate costs for corrective and rehabilitative health services for the under-fives with MESBDs, thus were excluded in this study. The occupational therapy clinics on the other hand, also as fixed capital costs occupied exceedingly small portions of the respective hospitals' floor plinths, hence valued as recurrent costs using prevailing local market prices for building spaces for renting.

Overhead costs: Overhead costs which consisted of staff emoluments, building space, administrative staff-time, and utility charges were proportionately allocated to the individual defects in addition to the cost drivers for respective interventions to calculate the total and unit economic costs of individual defects.

Estimation of the total and unit economic costs: The total economic costs of the outpatient services for all the defects were calculated by summing up direct and indirect costs known as final costs, whereas the unit economic costs of the outpatient services for all the defects was calculated as an average of the total costs. The final total costs were divided by the number of total cases (caseload) for all the defects and expressed in U.S Dollars **(Equations 7 and 8).** On the other hand, the total economic costs of the outpatient services for the individual defects were computed as the sum of costs of the interventions for individual defects and the proportionately allocated overhead costs to the individual defects. Subsequently, the unit economic costs of outpatient services for the individual defects were calculated based on average costs by dividing the total costs of the individual defects by the number of cases (caseload) and expressed in U.S Dollars **(Equations 7 and 8).** The overheads consisted of staff emoluments, building space, administrative staff-time, and utility charges, whereas the costs of the interventions included castings, bracings, tenotomies, physical and developmental therapies. The cost drivers for the interventions for congenital talipes equinovarus consisted of castings, bracings, tenotomies, and first visits in addition to review visits for the interventions which accounted for physical and developmental therapies aimed at achieving full functionality of the children with congenital talipes equinovarus. The cost drivers for the interventions for congenital pes planus on the other hand comprised castings and first visits in addition to reviewing visits for the interventions accounting for physical and developmental

therapies similarly aimed at achieving full functionality of the children with congenital pes planus, whereas the cost drivers for neural tube defects included first visits and review visits for physical and developmental therapies.

5.3 Results

The unit economic costs of corrective and rehabilitative outpatient health services for major external structural birth defects were estimated from a health care providers' perspective for a one-year time horizon using an ingredient approach.

5.3.1 Distribution of cases by category

Of 349 cases; 305 (87.39%) comprised of congenital talipes equinovarus (CTEV) comprising unilateral congenital talipes equinovarus 300 (85.96%), bilateral congenital talipes equinovarus 3 (0.86%), unilateral congenital talipes equinovarus with germ valgus 1 (0.29%), and congenital talipes equinovarus with spina bifida 1 (0.29%). Additionally, the study observed 35 (10.03%) cases of congenital pes planus (CPP), and 9 (2.58%) cases of neural tube defects (NTD) consisting of hydrocephalus 5 (1.43%), spina bifida 3 (0.86%), and spina bifida with hydrocephalus 1 (0.29%) **(Table 9).**

Table 9: Proportions of cases of major external structural birth defects

Groups of MESBDs	**Specific types of MESBDs**	**Frequency (%)**
Musculoskeletal system defects	Unilateral congenital talipes equinovarus	300 (85.96)
	Bilateral congenital talipes equinovarus	3 (0.86)
	Congenital pes-planus	35 (10.03)
	Unilateral congenital talipes equinovarus with spina bifida	1 (0.29)
	Unilateral congenital talipes equinovarus with germ valgus	1 (0.29)
Central nervous system defects	Spina bifida	3 (0.86)
	Spina bifida with hydrocephalus	1 (0.29)
	Hydrocephalus	5 (1.43)
Total cases		**349 (100.00)**

MESBDs, Major External Structural Birth Defects; %, Percent

5.3.2 Resource quantification for casting materials

Resource quantification for casting materials costing $3.9 used for two procedures consisted of Plaster of Paris Bandage (7.6cm×2.7m×2pcs), orthopaedic cotton bandage (15cm×3m×1pc), and glycerine oil (100 milliliters×1pc) costing $ 1.84, $1.22, and $ 0.82, respectively. A set of casting materials valued at $ 3.9 were used to cast two cases of clubfoot **(Table 10).**

Table 10: Identification, measurement, and valuation of casting resource inputs

Inputs for two castings	**Item description**	**Quantity**	**Unit costs (**$)
Plaster of Paris Bandage	7.6cm ×2.7m×2pcs	1	1.84
Orthopaedic Cotton Bandage	15cm ×3m	1	1.22
Glycerine Oil	100mls	1	0.82
Sub-total			**$3.9**

cm, Centimetres; m, Meters; mls, Millilitres; pcs, Pieces; $, USD

5.3.3 Estimation of direct and indirect costs for the outpatient services

The study approximated the direct costs of the outpatient services for MESBDs at $ 303,283.44 **(Table 11).**

Table 11: Direct costs for the outpatient services

Resources	**Item description**	**Quantity**	**Unit costs ($)**	**Total costs ($)**
Outpatient bracings	Leather foot cover, rubber sole, and a metallic rod	50 procedures	@ $ 15.31 per procedure	765.50
Outpatient tenotomies	Orthopaedic surgical procedure	14 procedures	@ $ 51.02 per procedure	714.28
Outpatient casting	Orthopaedic medical procedure	1089 procedures	@ $ 1.94 per procedure	2,112.66
First and review visits for castings	First and revisits	1089 visits	@ $10.2 per visit	11,107.80
First and revisits for all the defects	First and revisits	116 visits	@ $ 10.2 per visit	1,183.20
Emoluments	19 occupational therapists at the 4 study hospitals per month	19 @ $1,224.5 per month for 12 months	@ $1,224.5×19 ×12	279,072.00
Emoluments	4 support staff at the 4 study hospitals	4 @ $173.5 per month for 12 months	@ $173.5×4×12	8,328.00
Sub-total ($)				**303,283.44**

@ at; $, USD

The study also estimated the indirect costs of the outpatient services for MESBDs at $ 89,153.05 (**Table 12).**

Table 12: Indirect costs for the outpatient services

Resources	Item description	Quantity	Unit costs ($)	Total costs ($)
Estimated renting building space in square feet	898.44 (28.75×31.25) square feet @ $ 0.37 per square feet per hospital per month at 4 hospitals	898.44 @ $ 0.37 per square feet per month for 4 hospitals for 12 months	@ $0.37×898.44 ×4×12	15,956.29
Administrative staff-time	4 medical superintendents at the 4 study hospitals	4 @ $ 20.4 per day for 24 days for 12 months	$20.4×4×24 ×12	23,501.00
Administrative staff-time	4 chief nursing officers at the 4 study hospitals	4 @ $ 10.2 per day for 24 days for day for 12 months	@ $10.2×4×24 ×12	11,750.50
Administrative staff-time	4 health administrative officers at the 4 study hospitals	4 @ $ 10.2 per day for 24 days for day for 12 months	@ $10.2×4×24 ×12	11,750.50
Administrative staff-time	4 orthopaedic surgeons at the 4 study hospitals	4 @ $ 20.4 per day for 24 days for day for 12 months	@ $20.4×4×24 ×12	23,501.00
Utility	Water and sewerage	Estimated @ $ 25.51 per month for 4 hospitals	@ $25.51×4×12	1,224.48
Utility	Electricity	Estimated @ $ 30.61 per month for 4 hospitals	@ $30.61× 4×12	1,469.28
Sub-total ($)				**89,153.05**

@ at; $, USD

The study observed a total cost of $ 392,436.49 for 349 cases of MESBDs of which almost three-quarters (71.11%) of resource inputs were accounted for by emoluments of occupational therapists, whereas administrative staff-time accounted for about one-quarter (18%) **(Table 13).**

Table 13: Direct and indirect costs of the outpatient services

Costs	Description of resources	Total costs ($)	Percent (%)
Direct costs	Outpatient bracings	765.50	0.20
	Outpatient tenotomies	714.28	0.18
	Outpatient casting	2,112.66	0.54
	First and review visits for castings	11,107.80	2.83
	First and revisits for all the defects	1,183.20	0.30
	Occupational therapists' emoluments	279,072.00	71.11
	Support staff emoluments	8,328.00	2.12
	Sub-total ($)	**303,283.44**	**77.28%**
Indirect costs	Estimated renting building space in square feet	15,956.29	4.07
	Medical superintendent administrative staff-time	23,501.00	5.99
	Chief nursing officers' administrative staff-time	11,750.50	2.99
	Health administrative officers' administrative staff-time	11,750.50	2.99
	Orthopedic surgeons' administrative staff-time	23,501.00	5.99
	Water and sewerage utility charges	1,224.48	0.31
	Electricity utility charges	1,469.28	0.37
	Sub-total costs ($)	**89,153.05**	**22.72%**
	Grand total costs ($)	**392,436.49**	**100.00%**

@ at; $, USD; %, Percent

5.3.4 Distribution of overhead costs among the individual birth defects

The shared costs of the resource inputs consisted of staff-time, staff emolument, utility charges, and renting building space were approximated at $ 376,553.05 with emoluments for the occupational therapists accounting for almost three-quarters (74.11%), whereas staff-time costs accounted for 18.72% **(Table 14).**

Table 14: Distribution of overhead costs for specific birth defects

Inputs	Item descriptions	Total annual costs ($)	Percent (%)
Staff-time	Medical, orthopaedic surgeons nursing, and health administrative directors	70,503.00	18.72
Renting building space	Estimated in square feet	15,956.29	4.24
Emoluments	Occupational therapists	279,072.00	74.11
Emoluments	Support staff	8,328.00	2.21
Utilities	Water and sewerage	1,224.48	0.33
Utilities	Electricity	1,469.28	0.39
Total ($)		**376,553.05**	**100%**

$, USD; %, Percent

5.3.5 Proportional allocation of the overhead costs to the individual defects

To estimate the economic costs of the individual types of MESBDs in this study the overhead costs were allocated proportionally to the size (caseloads) of the individual defects **(Table 15).** The overhead costs were allocated proportionally (percentage-based) among the three specific cases: congenital talipes equinovarus (87.39%), congenital pes planus (10.03%), and neural tube defects (2.58%) **(Table 15).**

Table 15: Proportional overhead costs allocated to the specific birth defects.

Specific MESBDs	Defects with/without co-defects	Cases (%)	Overheads ($)
Congenital talipes equinovarus	Bilateral congenital talipes equinovarus, unilateral congenital talipes equinovarus, unilateral congenital talipes equinovarus with germ valgus, and unilateral congenital talipes equinovarus with spina bifida	305 (87.39%)	329,069.71
Congenital pes planus	Congenital pes planus	35 (10.03%)	37,768.27
Neural tube defects	Spina bifida, hydrocephalus, and spina bifida with hydrocephalus	9 (2.58%)	9,715.07
Total ($)		**349 (100.00%)**	**376,553.05**

$, USD; %, Percent

5.3.6 Total economic costs for outpatient services for the individual defects

The total economic costs for the individual defects were computed as follows; congenital talipes equinovarus was estimated at $ 343,959.87, whereas congenital pes planus and neural tube defects were estimated at $ 38,322.97 and $ 10,153.67, respectively **(Table 16).**

Table 16: Total economic costs for the individual defects

Resource inputs for CTEV with co-defects (n=305)				
Resource inputs	**Item description**	**Quantity**	**Unit cost ($)**	**Annual costs ($)**
Castings	Unilateral CTEV	1028	1.94	1,994.32
	Bilateral CTEV	27	1.94	52.38
	Unilateral CTEV with germ valgus	21	1.94	40.74
	Unilateral CTEV with spina bifida	11	1.94	21.34
First and review visits	Unilateral CTEV castings	1028	10.20	10,485.60
	Bilateral CTEV castings	27	10.20	275.40
	Unilateral CTEV with germ valgus castings	21	10.20	214.20
	Unilateral CTEV with spina bifida castings	11	10.20	112.20

Bracings	Unilateral CTEV	50	15.31	765.50
Review visits	CTEV and co-defects bracings	21	10.20	214.20
Tenotomies	Unilateral CTEV	14	51.02	714.28
Overheads	CTEV	305	1,078.92	329,069.71
Total ($)				**343,959.87**
Resource inputs for congenital pes planus (n=35)				
Castings	Congenital pes planus	2	1.94	3.90
Visits for castings	Congenital pes planus	2	10.20	20.40
Review visits	Congenital pes planus	52	10.20	530.40
Overheads	Congenital pes planus	35	1,079.09	37,768.27
Total ($)				**38,322.97**
Resource inputs for neural tube defects (n=9)				
First and review visits	Hydrocephalus	26	10.20	265.20
	Spina bifida	16	10.20	163.20
	Spina bifida with hydrocephalus	1	10.20	10.20
Overheads	Spina bifida with hydrocephalus	9	1,079.45	9,715.07
Total ($)				**10,153.67**

CTEV, Congenital Talipes Equinovarus; n, sub-total number of observations

5.3.7 Unit economic costs for the outpatient services for the defects

Equations 7 and 8 were adopted and computed the unit economic costs as follows: - $ 1,124.46 for all the defects, whereas congenital talipes equinovarus, congenital pes planus, and neural tube defects were approximated at $ 1,127.74, $ 1,094.94, and $ 1,128.19, respectively **(Table 17).**

5.3.8 Uncertainty analysis

Distortion of the health markets in the pricing of the medical goods and services, as well as changes in prices, the scantiness of the costs data, and methods of collecting data for the cost analysis study, underscore uncertainty analysis in economic evaluation studies to ensure validity and reliability of the results. Thus the estimated economic costs were inflated to the U.S Dollar Consumer Price Index (CPI) for a one-year time horizon from January 2018 to December 2018 to ensure the robustness of the cost analysis studies for the outpatient services for major external structural birth defects in the region (CPI, 2020). Notably, the Consumer Price Index was preferred in this study because it measures the mean changes in market prices over some time in which consumers pay for goods and services thus adjusting the economic costs to the Purchasing Power Parity globally (Briggs et al., 1994; CPI, 2020).

Consequently, the total annual economic costs for all major external structural birth defects that presented for the outpatient services in the region were approximated at $ 397,765.72, whereas the unit economic costs for at least one major external structural birth defect were estimated at $ 1,139.73. Similarly, the total annual economic costs for congenital talipes equinovarus congenital, pes planus and neural tube defects were estimated at $ 348,630.80, $ 38,843.39, and $ 10,291.56, respectively. On the other hand, the unit economic costs were approximated at $ 1,143.05 for congenital talipes equinovarus, $ 1,109.81 for congenital pes planus, and $ 1,143.51 for neural tube defects. **(Table 17).**

Table 17: Uncertainty analysis of the economic costs

Caseloads (Morbidity data)		**Unadjusted costs**		**Adjusted costs to CPI**	
Type of cases	**Frequency (n)**	**Annual total economic costs ($)**	**Unit economic costs ($)**	**Annual total economic costs ($)**	**Unit economic costs ($)**
All MESBDs	349	392,436.49	1,124.46	397,765.72	1,139.73
CTEV	305	343,959.87	1,127.74	348,630.80	1,143.05
CPP	5	38,322.97	1,094.94	38,843.39	1,109.81
NTD	9	10,153.67	1,128.19	10,291.56	1,143.51

MESBDs, Major External Structural Birth Defects; CTEV, Congenital Talipes Equinovarus; CPP, Congenital Pes Planus; NTD, Neural Tube Defects; CPI, Consumer Price Index Calculator

The study showed relatively similar unit economic costs of the defects despite wide variations among the caseloads for specific types of MESBDs **(Figure 8).**

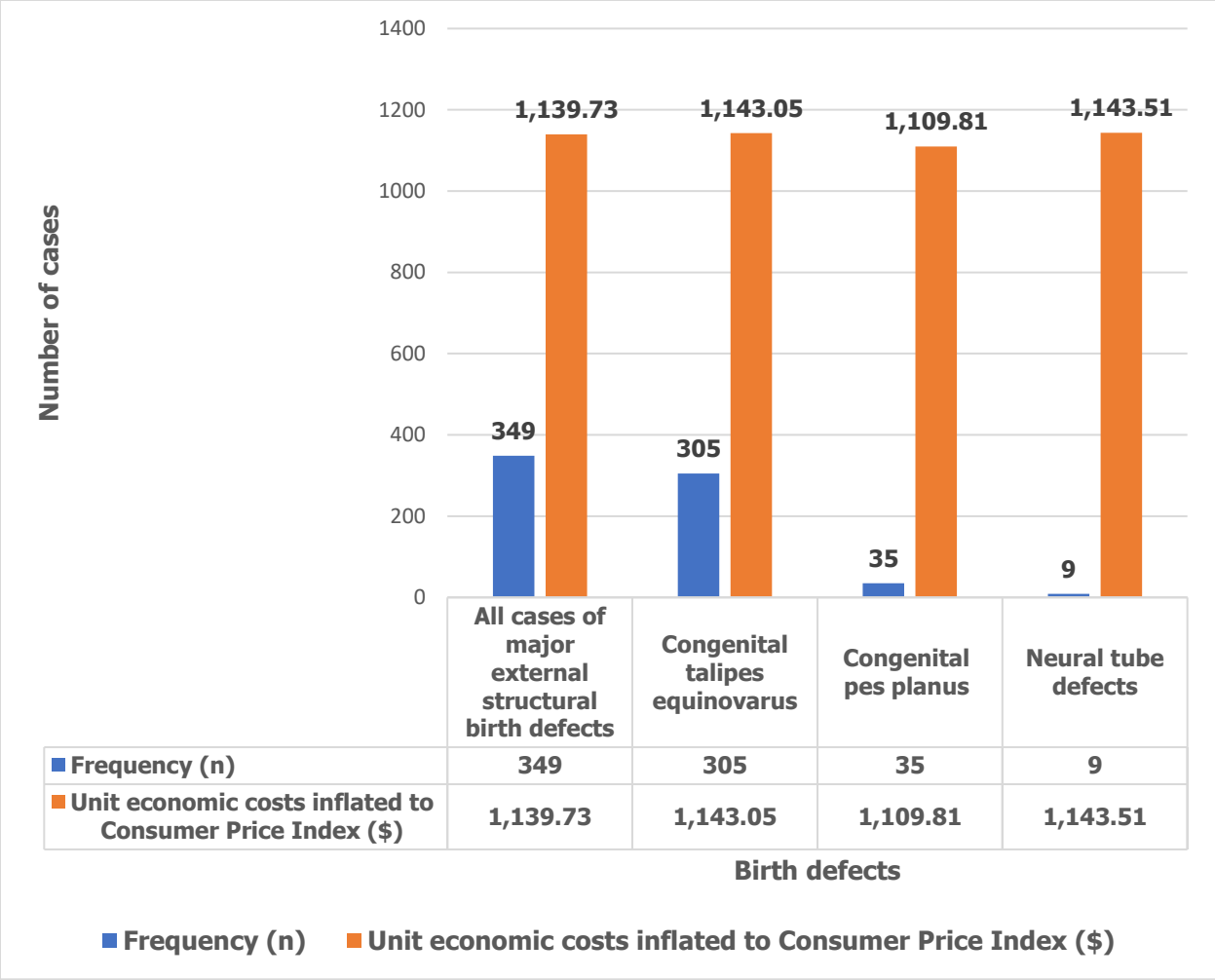


Figure 8: Bar graph for the adjusted unit economic costs of MESBDs, 2018

5.4 Discussions

To my knowledge, this was the first study to estimate the unit economic costs of MESBDs from health care providers' economic perspective among the under-five-year-old children in Kiambu County, Kenya. Substantial public health resources are continually allocated to the health care systems for the care of children with MESBDs, however, the unit economic costs of care are barely known because they are rarely estimated mainly in the developing countries (Khurmi et al., 2014; Waitzman et al., 1994). Sufficient access and utilization of corrective and rehabilitative health services remain an important public health intervention for improving the quality of life for birth defect-affected children globally (Christianson et al., 2005, 2006; WHO, 2014, 2020). Even though limited cost data, inadequate costing expertise, and the rarity of defects have been attributed to the lack of knowledge on their costs, it is of public health and economic interest to estimate the opportunity costs of health care services for MESBDs (Khurmi et al., 2014; Waitzman et al., 1994).

The results of this study could provide a baseline unit economic costs for the corrective and rehabilitative health services, inform the efficient allocation of health resources, stimulate, and inform cost studies, especially the costs' arms of full economic evaluation analyses (Birch & Gafni, 1996; Cunningham, 2000; Drummond et al., 2015).

The study encountered 349 cases consisting of 305 (87.39%) cases of CTEV, 35 (10.03%) cases of CPP, and 9 (2.58%) cases of NTD. Congenital talipes equinovarus consisted of 300 (85.96%) cases of unilateral CTEV, 3 (0.86%) cases of bilateral CTEV, 1 (0.29%) case of unilateral CTEV with germ valgus, and 1 (0.29%) case of CTEV with spina bifida. Neural tube defects on the other hand comprised 5 (1.43%) cases of hydrocephalus, 3 (0.86%) cases of spina bifida, and 1 (0.29%) case of spina bifida with hydrocephalus. Despite variations in the number of cases (caseloads) observed for each of the defects mentioned above, this study showed a relatively similar unit economic cost for each defect in the county. The unit economic costs for NTD were approximated at $ 1,143.51, whereas CTEV, and CPP were valued at $ 1,143.05, and $1,109.81, respectively. Notably, the unit economic cost of providing corrective and rehabilitative outpatient health services for these defects was collectively approximated at $ 1,139.73.

Despite defects of the central nervous system contributing the least number (9) of cases compared to congenital talipes equinovarus (305), and congenital pes planus (35), its unit economic costs were relatively equivalent to the costs of the latter two types of the MESBDs observed in the county. Although some forms of neural tube defects are potentially fatal, the children who survive beyond infancy require substantial economic resources to deal with the related adverse health impacts (Christianson et al., 2005, 2006; Waitzman et al., 1994; Wu et al., 2013). The results of this study were consistent with other study findings in the region and across the world that the greatest burden of disease associated with MESBDs is usually accounted for by the defects of the central nervous system (Bowles et al., 2014; Ouyang et al., 2007; Wu et al., 2013). The economic burden of spina bifida is substantial throughout the life of the affected individuals ascribed to the experienced high medical care expenditures in the early years of life with the defect and later due to reduced milestone development (Bowles et al., 2014; Rofail et al., 2013). This study similarly showed that neural tube defects followed by congenital pes planus accounted for the highest

disease burden associated with MESBDs being shouldered by the health care systems in Kiambu county.

Even though this study estimated the economic costs of these defects among the under-five-year-old children, my findings mimicked results of other studies such as in Germany where similarly high staggering economic costs were encountered among the general population with various forms of NTD between 2006 and 2009 (Bowles et al., 2014). Worldwide, spina bifida has singly been observed to account for the highest-burden of disease among other types of MESBDs (Bowles et al., 2014; Wu et al., 2013). Significant economic costs have been reported among new-born children with NTD during their first years of life, whereas high healthcare expenditures have been observed during childhood, adolescents, and adulthood compared to the children without NTD globally (Bowles et al., 2014). In Germany, the average annual health expenditure of persons with spina bifida was estimated at € 4,532, with inpatient health services contributing €1,358 (30.0%), outpatient health services € 644 (14.2%), rehabilitation health services € 29 (0.6%), drug therapy € 562 (12.4%), and other remedies € 1,939 (42.8%) (Bowles et al., 2014). In the United States among children aged between 1-17 years old, medical expenditures on spina bifida were estimated to cost 13 times compared to medical expenditures on children without spina bifida (Ouyang et al., 2007).

Notably, annual direct economic costs of different forms of major birth defects were estimated at $ 2.6 billion in 2004 in the United States of America (Mburia-Mwalili & Yang, 2014; Tinker et al., 2015). Nonetheless, this study also endeavoured to find and estimate the annual direct economic cost of MESBDs at $ 397,765.72. The defects encountered at the study hospitals consisted of neural tube defects, congenital talipes equinovarus, and congenital pes planus. Despite different socioeconomic and demographic characteristics in Kenya and U.S being developing and developed countries respectively, this was a remarkable empirical effort to estimate the direct economic costs of MESBDs in Kiambu County. Cost studies were pioneered in the United States of America by Dorothy Rice in 1967, and have since been undertaken widely in Europe and Australia unlike in the middle- and low-income economies (Mugisha et al., 2002). Low undertakings of cost studies, particularly in low-and middle-income economies have been attributed to the scarcity of data on the burden of these defects (Conteh & Walker, 2004; Gedefaw

et al., 2018; Khurmi et al., 2014). Thus, the variations of annual direct economic costs could have been due to differences in the availability of the cost data, costing expertise, health services access, and utilization (economies of scale) (Drummond et al., 2015; Mburia-Mwalili & Yang, 2014; Mugisha et al., 2002; Tinker et al., 2015). Despite variations observed in the estimates of the economic costs, these findings point to the continuous disease burden associated with MESBDs in the county underpinning efficiency in resource utilization, and allocation for MESBDs in public and faith-based health facilities.

The few cases of NTD observed in this study could be attributed to a proportion of the carers of children with NTD seeking alternative therapies due to the associated adverse psychosocial effects experienced by the affected families (Kronenberger & Thompson Jr, 1992; Rofail et al., 2013, 2014; Tracey Smythe et al., 2017; Vermaes, Janssens, Bosman, & Gerris, 2005; Wallander et al., 1989). Thus, the economic costs of NTD would otherwise be exponential compared to other forms of MESBDs observed in the study if all carers would have sought care from the respective study hospitals. Nevertheless, the estimated costs demonstrated the potential catastrophic burden of the 'silent' economic problem in the region, thus underscoring more scientific efforts to understand the magnitude of MESBDs regionally (Waitzman et al., 1994). The observations made by this study have contradicted the epidemiological and economic fallacy that MESBDs are not of public health priority relative to other health events especially in resource-constrained countries (Christianson et al., 2005, 2006; WHO, 2014, 2020). Nevertheless, some limitations were inherent in this study; first and foremost, medical records used to draw the cost data were not designed for economic evaluation studies, whereas some of the defects were likely to delay childhood milestone development prolonging the demand for corrective and rehabilitative outpatient service possibly leading to more economic expenditures. The researchers also experienced difficulties in distinguishing the extent of the cost drivers for congenital talipes equinovarus occurring with spina bifida, congenital talipes equinovarus occurring with germ valgus, and spina bifida occurring with hydrocephalus, potentially due to inaccuracies of the profiled cost data.

5.5 Conclusions and recommendations

This study estimated the economic costs of outpatient corrective and rehabilitative health services for MESBDs in Kiambu County in Kenya. Despite the fewest cases of NTD, the study showed that NTD was associated with the highest burden of disease followed by CPP in the county.

Although CTEV proportionally contributed the highest caseload for the defects, it essentially accounted for the lowest burden of the disease associated with MESBDs in the county. This observation thus points to adverse developmental, and psychosocial impacts among the affected children and their families who are not able to access corrective and rehabilitative services for the defects. Similarly, these findings suggest a possible reduced economic productivity among the affected families arising from direct and indirect costs associated with MESBDs. Therefore, I would like to recommend further studies on the direct and indirect economic costs of MESBDs among children of school-going age to understand the impacts. The study also observed that salaries and benefits of the occupational therapist were the major cost drivers for the outpatient services accounting for more than 70% of the total costs of major external structural birth defects. Thus, we recommend efficient resource allocation for occupational and rehabilitative health services to minimize expenditures on staff salaries and benefits in Kiambu County, Kenya.

CHAPTER SIX: GENERAL DISCUSSIONS, CONCLUSIONS, AND RECOMMENDATIONS

6.1 General discussions

To the best of my knowledge, this was the first study to quantify the public health and economic burden of MESBDs in Kenya. The study estimated the prevalence, investigated the determinants, and approximated the economic costs of MESBDs to address the knowledge gap and generalization of the results to similar settings in Kiambu County and the region. The study observed an upward five-year prevalence trend of six groups and 29 specific types of MESBDs affecting the musculoskeletal, central nervous, orofacial, genital, ocular, and anal body organ systems. It showed that defects of the musculoskeletal and central nervous systems were the most prevalent MESBDs in the county; an observation consistent with other research findings in Kenya, Ethiopia, Tanzania, and South-East Asia (Gedefaw et al., 2018; Githuku et al., 2014; Kishimba, Mpembeni, Mghamba, et al., 2015; Lund et al., 2009; Muga et al., 2009; Onyango & Noah, 2005; WHO, 2013, 2014, 2018, 2020; Wu et al., 2013). Defects of the musculoskeletal system were reported as the most common with a prevalence trend ranging from 22.98 (95% CI: 11.87-40.13) to 116.9 (95% CI: 92.98-145.08) per 100000 live births between 2014 and 2018. This was followed by the defects of the central nervous system with a prevalence trend ranging from 13.40 (95% CI: 5.39-27.61) to 32.79 (95% CI: 20.79-49.19) per 100000 live births from 2014 to 2018.

Congenital talipes equinovarus (clubfoot) was noted as the most frequent among defects of the musculoskeletal system and 29 types of the defects during the study period; findings corroborated by a study conducted in 1984 in Kenya (Muga et al., 2009). Worldwide, clubfoot has been reported to occur in two forms, namely severe syndromic and idiopathic with idiopathic being the most frequently occurring clubfoot as isolated defects or associated with minor defects (Pavone et al., 2012). The severe syndromic form on the other hand is characterized by sacral agenesis (arthrogryposis), spina bifida, and/or muscular atrophy among other anomalies (Pavone et al., 2012). Additionally, severe syndromic clubfoot could be associated with congenital hip dislocations, joint laxities, tibial torsions, foot defects, and lack of some tarsal bones (Pavone et al., 2012). This study made similar observations and reported 85.96% cases of unilateral clubfoot (idiopathic clubfoot), 0.86% cases of bilateral clubfoot (idiopathic clubfoot), unilateral clubfoot

with spina bifida (severe syndromic clubfoot) (0.29%), and clubfoot with germ valgus (idiopathic clubfoot) (0.29%).

Familial history of clubfoot, foot anomalies, siblings' history of clubfoot (recurrence), sex of the child, and maternal smoking are some of the factors associated with an idiopathic clubfoot which was observed as the most prevalent during the study period (Pavone et al., 2012). Although this study did not show a significant statistical relationship specific to clubfoot with the above-mentioned predictors of idiopathic clubfoot, it observed that children whose preceding siblings were born with any form of birth defects were most likely to be born with MESBDs compared to those without a similar history. This study also observed three cases of clubfoot among siblings with a history of clubfoot pointing to recurrence of the defects among siblings. Further, the study observed single cases of foot aversion, internally rotated hand, and congenital scoliosis like other findings. These observations corroborated results from other studies that positive familial histories of birth defects, familial histories of clubfoot, sibling histories of clubfoot, and familial histories of foot anomalies are associated with the occurrence of clubfoot in children (Pavone et al., 2012). These observations pointed to the genetic and multifactorial etiology of clubfoot among defects of the musculoskeletal system and defects of other body organ systems (Pavone et al., 2012).

Defects of the central nervous system were also observed in this study and noted as the second most prevalent among MESBDs during the study period corroborated by a study in Ethiopia (Gedefaw et al., 2018). However, defects of the central nervous systems were observed as the most common at selected hospitals in Tanzania (Kishimba, Mpembeni, & Mghamba, 2015). Even though adequate dietary micronutrients and folic acid intake during the maternal reproductive period in addition to iron-folic acid supplementation during the periconceptional period are known to prevent the occurrence of central nervous system defects, this study did not show a statistically significant relationship with the defects (Gedefaw et al., 2018; Green, 2002; Hage et al., 2012; Williams et al., 2015). Similarly, the study neither showed a significant relationship between MESBDs with gestational age at first antenatal visit nor trimester the antenatal care began; the proximal factors known to influence periconceptional iron-folic acid supplementation among the women of reproductive age. These observations could be attributed to disparate maternal exposure

to environmental teratogens, socioeconomic endowments, sociodemographic characteristics, and genetic predispositions in the region (Christianson et al., 2005, 2006; Gedefaw et al., 2018; Kishimba, Mpembeni, & Mghamba, 2015; Kishimba, Mpembeni, Mghamba, et al., 2015; WHO, 2014, 2020).

Positive familial history of the central nervous system defects has been reported to increase the occurrence of the same defects by 2-5% (El Koumi et al., 2013; Florentina Mashuda, 2014). Similarly, other research findings have approximated recurrence of the central nervous defects by 3-5 times among families with a positive history of the defects (Kondo et al., 2017). Notably, familial history of spina bifida, use of antiepileptic drugs without folic acid supplementation, low birthweight $\leq$ 2500 grams, and lack of folic acid supplementation during four weeks before conception and twelve weeks after have been associated with the occurrence of spina bifida (Kondo et al., 2017). This study however showed a significant relationship between a history of siblings with birth defects and MESBDs thus alluding to the occurrence of central nervous system defects of genetic etiology in the region. Although female children have been associated with the occurrence of defects of the central nervous system, this study did not show a significant relationship between the sex of the child with MESBDs (Kondo et al., 2017). Sex of the child and consanguineous marriages have been noted to be among the predictors of central nervous system defects of the genetic etiology (Kondo et al., 2017). The national census carried out in Kenya in 2019 showed six domains of disability consisting of visual, hearing, mobility, cognition, self-care, and communication among children aged five years attributable to MESBDs largely affecting more females compared to their counterparts (KNBS, 2019; Kondo et al., 2017). Even though albinism which is a genetically acquired functional birth defect mostly affecting the females compared to males was also reported by the 2019 National census could act as a marker for MESBDs in Kiambu County (KNBS, 2019; Kondo et al., 2017).

This study also observed orofacial clefts as the third most common, an observation corroborated by other study findings in the region (Agbenorku, 2013; Onyango & Noah, 2005). The prevalence of syndromic orofacial clefts has been associated with the increased number of women giving birth aged beyond 35 years in settings without community education, prenatal detection, universally

accessible family planning services, and related services attributed to chromosomal anomalies (Christianson et al., 2005, 2006; El Koumi et al., 2013; Gill et al., 2012; Mashuda et al., 2014). Family planning services, clinical genetic services, and periconceptional health services could effectively prevent the occurrence of down syndrome, and orofacial clefts associated with chromosomal abnormalities; orofacial clefts and neural tube defects associated with single gene defects and environmental factors, as well as alcoholic syndromes, congenital syphilis, and congenital rubella syndrome attributed to environmental factors (Christianson et al., 2005, 2006). Notably, this study observed imperforate anus, congenital cataract, anophthalmia, malformed penis, unformed genitalia, epispadias, and hypospadias; some of the extremely rare defects attributed to multiple etiological factors. Thus acted as a pointer to possible latent major internal birth defects detectable later after birth by advanced medical techniques hence underscoring the importance of the defect-responsive health care systems in the region (Christianson et al., 2005, 2006; Lund et al., 2009; Parker et al., 2010; Romitti, 2007; Sever, 2004; van der Horst & de Wall, 2017; WHO, 2014, 2020).

The prevalence of defects varies by types and severity from one country to another even among the regions within the same countries and communities with similar occupations and social status (Christianson et al., 2005, 2006; Mashuda et al., 2014; D. Mekonnen & Worku, 2021; Taye et al., 2016, 2019; WHO, 2020). These research findings were corroborated by this study observing that the likelihood of the women who conceived while living at Ruiru sub-county was higher than those who conceived while living in other sub-counties within Kiambu County. On the other hand, the women who got pregnant while residing in Kiambu sub-county were less likely to give birth to children with MESBDs compared to those who got pregnant while living in other sub-counties within the same county. Apart from the environmental etiological factors, consanguinity, migrations, and intermarriages could also be associated with varying regional prevalence of defects of the genetic etiology (Christianson et al., 2005, 2006).

Further, this study showed that substantial resources approximated at $ 397,765.72 were invested by the county government in the outpatient occupational therapy clinics to provide tenotomies, castings, bracings, physical and developmental therapies for children who were born with

congenital orthopedic conditions in 2018 in the county. The health department spent about $ 348,630.80 for the outpatient care of 305 cases of clubfoot, $ 38,843.39 on 5 cases of congenital pes planus, and $ 10,291.56 on 9 cases of neural tube defects during the same time. Consequently, the government spent nearly $ 1,139.73 to treat at least one case of congenital orthopedic defects in the outpatient occupational therapy clinics in the region. Further, the study observed that the expenditures by the county government on clubfoot were estimated at $ 1,143.05, $ 1,109.81 for pes planus, and $ 1,143.51 for neural tube defects. These costs would otherwise be catastrophic if such costs were to be borne by the affected individual households, thus underscoring the significance of universal health care in the region. The findings of this study could inform health planning, resource allocation, and utilization of outpatient occupational therapy services within the region.

The county's health department however required high substantial resources to treat a single case of central nervous defects as an outpatient compared to defects of the musculoskeletal system. This observation was consistent with other study findings reporting that the highest-burden of disease associated with MESBDs is usually accounted for by the defects of the central nervous system (Tracey Smythe et al., 2017; Yi, Lindemann, Colligs, & Snowball, 2011). Nevertheless, some limitations were inherent; first and foremost, unordered filing of maternity files compounded by heaped pools and sometimes defaced files could have led to health statistics unreliability, and medical records inaccuracies resulting in underreporting of cases and eventually underestimation of the public health magnitude of these anomalies in the county. However, this phenomenon was deliberately reduced by gathering information from every file at a time until all the files were reviewed to determine the prevalence numerator. Additionally, the study collected all the cases of birth defects recorded by the providers in the maternity files, maternity registers, and neonatal files; and used a predefined inclusion criterion to determine the prevalence numerator for this study. Secondly, the possibility of differential recall bias between the cases and controls arising from different psychosocial experiences of births with and/or without defects was reduced by including only under-five years old children in this study. Thirdly, although data on cost drivers for the outpatient occupational therapy services were barely kept by the health care systems, studies endeavored and gathered all information related to this study to inform the economic

evaluation of the interventions that consisted of tenotomies, bracings, castings, physical and developmental therapies.

6.2 Conclusions and recommendations

Worldwide, the prevalence of the most common MESBDs consisted of defects of the musculoskeletal system, central nervous system, and orofacial defects among other defects. The prevalence trends for these defects were noted to be on an upward trend during the study period between 2014 – 2018 attributed to disparate multiple etiological factors. The study also observed some of the very rare defects on an upward trend during the study period which could be associated with latent major internal structural birth defects. The study further noted that the county government spent substantial resources on the congenital orthopedic outpatient cases which would otherwise be catastrophic if the costs were to be borne by the individuals. Defects of the central nervous system were observed to account for the highest economic burden associated with MESBDs in the county followed by those of the musculoskeletal system. Conversely, defects of the musculoskeletal system accounted for the highest public health burden followed by those of the central nervous system, and orofacial clefts in that order in the region. The findings of this study could persuade health planners and policymakers to recognize MESBDs as a public health problem in the region. This would influence investment in preventive actions for these defects and improve access to outpatient occupational therapy services by the county governments underscoring the following recommendations: -

1. The establishment of hospital-based surveillance systems for the most prevalent defects affecting the musculoskeletal, and central nervous systems as well as those affecting orofacial, genital, ocular, and anal organs in the region. The hospital-based surveillance system is recommended because it requires fewer resources compared to the population-based to enhance understanding of the public health burden of such defects in the region. This would aid routine assembly and analysis of the local epidemiological data to monitor the distribution, trends, and patterns of the emerging and re-emerging defects. The hospital-based surveillance system would also help to elucidate the etiological factors, assess the treatments strategies, and evaluate the prevention measures for these defects in the region.
2. The establishment of a national birth defects database by linking the hospital-based epidemiological data on birth defects including prevalence numerator and the national

prevalence denominator consisting of live births and stillbirths at the civil registration bureau. This could be achieved through the formulation of legislative and/or policy frameworks aimed at incorporating sections for entering the types of defects the child is born with birth notifications forms by health care providers as registration assistants at the health facilities. On the other hand, home births with clinically obvious defects should not be notified at community levels by assistant chiefs; instead, should be linked to health facilities by the community health assistants for care and birth notifications. Subsequently, this would ensure that birth registrations and birth certificates issued by the national civil registration bureau contain complete epidemiological data that would be used to estimate regional and national public health magnitude of major external structural birth defects. Thus provide a snapshot of the problem from time to time to inform public health planning, and budgeting and allocation health resources for defect-specific services as well as stimulate public health studies for birth defects in the region.

3. Hospital-based epidemiological studies to understand the public health burden of the most common sub-types of major external structural birth defects including spina-bifida (thoracic, lumbar, cervical, and sacral), talipes (equinus, valgus, varus, and calcaneus), hypospadias (sub-coronal/proximal-penile, midshaft/mid-penile, and penoscrotal/distal-penile, among other defects. Epidemiological studies like surveillance systems would help define the local epidemiology, recognize the emerging cases, detect the epidemiological changes, and forewarn health care systems on the existing environmental hazards. Thus, influence formulation of risk-based surveillance systems, defect-specific preventive frameworks, and treatment strategies.
4. To conduct full economic evaluation studies of outpatient occupational therapy health services including cost-minimization, cost-effectiveness, cost-utility, and cost-benefit analyses to understand the burden from the individuals', providers', and societal perspectives, and inform policy decisions. Determining the costs and effects of health interventions for major external structural birth defects consisting of the monetary units, natural units, and healthy years would inform the contribution of the health care systems in dealing with adverse health impacts associated with the disease burden in the region. Similarly, a qualitative study to understand the psychological impact of major external structural birth defects among adolescents and their caregivers would be of public health significance in the region.

5. The study also alluded to birth defects of the genetic etiology underscoring integration of genetic clinical services including genetic counselling, genetic screening, prenatal diagnosis, and treatment with routine reproductive health services. Further interventions could comprise elective termination of pregnancies for foetal anomalies, as well as planning childbirths, and neonatal care for defect-affected pregnancies in the region.
6. The uniformity in the designs of maternity files to standardize collation and correlation of hospital-based epidemiological data by the primary health care providers to improve the accuracy of the medical records and reliability of the health statistics.
7. Redesigned outpatient occupational therapy registers to include fields (columns and rows) for recording the cost drivers for the tenotomies, bracings, castings, physical and developmental therapies along with morbidity data. This would inform the economic evaluation of health care programs for major external structural birth defects in the region.

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APPENDICES

Appendix 1: Data collectors training schedule

Title of Study: "The Epidemiology and Economic Burden of Major External Structural Birth Defects in Kenya: The Case of Kiambu County".

DAY I		
Time	**Topics**	**Facilitators**
8.00-8.30am	Reporting, and registration	All
8.30-9.00am	Introduction	Principal Investigator
9.00-10.00am	Description and detection of neural tube defects	Principal Investigator
10.00-10.30am	**Tea Break**	**All**
10.30-11.30am	Description and detection of abdominal wall defects	Principal Investigator
11.30-12.30pm	Description and detection of musculoskeletal system defects	Principal Investigator
12.30-1.30pm	**Lunch Break**	**All**
1.30-2.30pm	Description and detection of limb reduction defects	Principal Investigator
2.30-3.30pm	Description and detection of orofacial clefts	Principal Investigator
3.30-4.30pm	Description and detection of genital organ defects	Principal Investigator
4.30-5.00pm	Questions and Answers	All
5.00pm	**Departure**	**All**
DAY II		
8.00-9.00am	Reporting and registration	All
9.00-10.00am	Informed consent	Principal Investigator
10.00-10.30am	**Tea Break**	**All**
10.30-11.30am	Questionnaires and interviewing techniques	Principal Investigator
11.30-12.30pm	Extraction of data from antenatal booklets	Principal Investigator
12.30-1.30pm	**Lunch Break**	**All**
1.30-2.30pm	Extraction of data from MOH333	Principal Investigator
2.30-3.30pm	Extraction of data from maternity files	Principal Investigator
3.30-4.20pm	Extraction of data from neonatal files	Principal investigator
4.20-4.30pm	Extraction of data from daily bed returns (DBR)	Principal Investigator
4.30-5.00pm	Questions and Answers	All
5.00pm	**Departure**	**All**
DAY III		
8.00-9.00am	Reporting and registration	All
9.00-10.00am	Extraction of data from occupational therapy clinic registers	Principal Investigator
10.00-10.30am	**Tea Break**	**All**
10.30-11.30am	Extraction of data from antenatal booklets	Principal Investigator
11.30-12.30pm	Minimization of bias in observational studies	Principal Investigator
12.30-1.30pm	**Lunch Break**	**All**
1.30-2.30pm	Prevalence data abstraction tool	Principal Investigator
2.30-3.30pm	Cost analysis data abstraction tool	Principal Investigator
3.30-4.30pm	Data entry into the abstraction tools	Principal Investigator
4.30-5.00pm	**Questions, Answers and Departure**	**All**

Appendix 2: Parent participant informed consent form

Title of Study: "The Epidemiology and Economic Burden of Major External Structural Birth Defects in Kenya: The Case of Kiambu County".

Principal Investigator
Mr. Agot, George Nyadimo, BSc. (Nursing Sciences); Advanced Diploma (Public Health); MSc. (Health Economics and Policy); Chief Nursing Officer and Nursing Services Manager, Pumwani Maternity Hospital, Directorate of Health Services, Nairobi Metropolitan Services, Executive of Presidency, Republic of Kenya

Institutional Affiliation: The University of Nairobi, School of Public Health

Course: Doctor of Philosophy Degree in Public Health (Ph.D.)

Co-Investigators and Institutional Affiliations

1. **Dr Marshal, M. Mweu,** BVetMed; PGDip. (Epidemiology); MSc. (Epidemiology); Ph.D. (Epidemiology); Lecturer, Epidemiology and Biostatistics, School of Public Health, University of Nairobi
2. **Prof Joseph, K. Wang'ombe,** BA; MA; Ph.D. (Health Economics); Professor of Health Economics and Policy Development, School of Public Health, University of Nairobi

Introduction

I would like to tell you about a study being conducted by the above-listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent. Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in medical research: (i) Your decision to participate is entirely voluntary (ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal (iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? Yes / No

This study has been approved by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee: **Protocol No. Ref: KNH-ERC/A/44**

What is this study about?

The researchers listed above are interviewing mothers whose children are born with major external structural birth defects in Kiambu County between 1st January 2014 and 31 December 2018. The purpose of the interview is to find out how frequent are these defects and what are the risk factors and how much is the economic costs of providing care to these children in Kiambu County. Participants in this research study will be asked questions about their socio-economic, health-

related, behavioural, environment-related, and knowledge factors. There are approximately 408 participants in this study randomly chosen who will be asked the same questions mentioned above. We are asking for your consent to consider participating in this study.

What will happen if you decide to be in this study?

If you agree to participate in this study, the following things will happen: You will be interviewed by a trained interviewer in a private area where you feel comfortable answering questions, the interview will last approximately 30 minutes, the interview will cover topics such as level of education, marital status, occupation, age, and sex of your child with the defect, birth order of the child with a birth defect, alcohol use, indoor smoke, and pesticide exposure among others. After the interview has finished, if you require counseling, I will provide a trained counselor in a private and comfortable room for you. We will ask for a telephone number where we can contact you if necessary. If you agree to provide your contact information, it will be used only by people working for this study and will never be shared with others. The reasons why we may need to contact you include clarifying some of the information you will have given and not clear to me.

Are there any risks, harms, or discomforts associated with this study?

Medical research has the potential to introduce psychological, social, emotional, and physical risks. Efforts will always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a coded number to identify you in a password-protected computer database and will keep all our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be full-proof secure, so it is still possible that someone could find out you were in this study and could find out information about you. Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse to participate in the interview or any questions asked during the interview. It may be embarrassing for you to ask some questions; however, we will do everything we can to ensure that this is done in private. Furthermore, all study staff and interviewers are professionals with special training in these examinations/interviews. Also, some information about the child may be stressful and not easy to recall, however, I request you provide the most correct responses to the best of your ability.

Are there any benefits to being in this study?

You may benefit by receiving free counseling when needed and health information, as necessary. We will refer you to a hospital for care and support where necessary. Also, the information you provide will help us better understand the frequency, risk factors, and costs of these defects. This information is a contribution to science and policy formulation on the prevention, control, rehabilitation, and treatment of children born with structural birth defects.

Will being in this study cost you anything?

Not at all, you will not be asked to pay anything for participating in this study and you will not be refunded any money for participating in this study.

What if you have questions in the future?
If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page. For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Extension 44102, and email address: uonknh_erc@uonbi.ac.ke. The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

What are your other choices?
Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

Participant's statement
I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study. I understand that all efforts are made to keep information regarding my identity confidential. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study: **Yes / No**
I agree to provide contact information for follow-up: **Yes/No**
Participant Printed Name: _____
Telephone Number: _____
Participant Signature / Thumb Stamp: _____Date _____
Researcher's statement
I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant understood and has willingly and freely given his/her consent.

Researcher's Name: _____Date: _____

Signature: _____

Role in the study: _____ [i.e., study staff who explained informed consent form.]

For more information contact 0721589544 at any time from 8.00 am to 5.00 pm

Appendix 3: Numerator data abstraction tool

Study Title: "Prevalence of Major External Structural Birth Defects in Kiambu County, Kenya, 2014-2018"

Instructions to research assistants

i. Record cases of structural birth defects as described or defined in the maternity files, maternity registers (MOH333), newborn unit files, and neonatal daily-bed returns
ii. Complete all fields accurately

Date: _____

Name of Hospital: _____

Name of Research Assistant: _____

Months of Data Records: _____
Types of Data Source: _____
Name of Hospital of Birth: _____
IP/NO: _____
Year: _____
Date of Admission: _____
Number of ANCs Attended: _____
Mother's Name: _____
Village/Residence: _____
Mother's Age: _____
Marital Status: _____
Parity: _____
Gravidity: _____
Last Menstrual Period: _____
Expected Date of Delivery: _____
Date of Birth: _____
Sex: _____
Birth weight: _____
Name of defects: _____
Referred to: _____
Referred from: _____
Comments:
_____
_____
_____

Appendix 4: Structured, pretested, interviewer-administered questionnaire

Study Title: "Risk Factors for Major External Structural Birth Defects in Kiambu County, Kenya: A Case-Control Study"

Date……

Case Id/No ……

Instructions

i. These questions are to be administered by research assistants to mothers of children with and without MESBD **(cases and controls)** respectively
ii. Fill in the correct responses in spaces provided in the questionnaire
iii. Tick the correct response(s) for each multiple-choice question as necessary
iv. Ask these questions about the maternal periconceptional period (twelve weeks before conception and eight weeks after conception)

Part one: Question(s) for case subjects ONLY

Name(s) of the birth defect (s)…….

Part two: Sociodemographic-environmental factors (Questions for case and control subjects)

1. Maternal age at the conception of the current child in completed years……
2. Maternal sub-county of residence at the conception of the current child in Kiambu County……
3. Maternal level of education at the conception of the current child
    a. None
    b. Primary
    c. Secondary
    d. College certificate
    e. College diploma
    f. University degree
4. Maternal occupation at the conception of the current child…….....
5. Mother's religion
    a. Christianity
    b. Islamic

6. Marital status
    a. Single
    b. Married
    c. Separated
    d. Divorced
    e. Widowed
7. Paternal age at the conception of the current child in completed years…….
8. Did you plan for the last pregnancy (current birth)?
    a. Yes
    b. No
9. Started using folic acid at least three (3) before the last date of the menstrual period.
    a. Yes
    b. No
10. Started ANC eight weeks after the last date of a menstrual period in the last pregnancy **(trimester ANC care began)**
    a. Yes
    b. No
11. Indicate the date of the last menstrual period in the last pregnancy **(date/month/year; obtain from ANC booklet)** ……...
12. Indicate the date of the first antenatal clinic visit of the last pregnancy **(date/month/year; obtain from ANC booklet)** ……...
13. Date of birth of the current child (**date/month/year; obtain from ANC booklet)** ……

Part three: Multifactorial inheritance (Questions for case and control subjects)

14. Parity **(from ANC booklet)** …….
15. Nature your last pregnancy
    a. Single
    b. Multiple
16. Sex of the current child if single pregnancy……
    a. Male
    b. Female

17. Specify sex of the twin in multiple pregnancies……

    a. Male
    b. Female

18. Another sibling with a birth defect

    a. Yes
    b. No

19. If there is another sibling with a birth defect, name or describe the defect(s)……

Part four: Environmental teratogens (Questions for case and control subjects)

20. Name of chronic illness

    a. None
    b. Diabetes
    c. Hypertension
    d. Epilepsy
    e. Others…….

21. Names of medicine you used during the last pregnancy……

22. You sprayed the farms with pesticides during the last pregnancy.

    a. Yes
    b. No

23. Smoked cigarette during the periconceptional period (3 months before pregnancy and 2 months after pregnancy)

    a. Yes
    b. No

Appendix 5: Costs data abstraction tool (Resource quantification)

Study Title: "Cost Analysis of Outpatient Services for Major External Structural Birth Defects: An Ingredient Approach in Selected Hospitals in Kiambu County, Kenya"

S/No	Resource inputs	Item description	Quantity	Unit costs ($)	Total costs ($)
1.	Outpatient bracings	Leather foot cover, rubber sole, and a metallic rod			
2.	Outpatient tenotomies	Orthopaedic surgical procedure			
3.	Outpatient casting	Orthopaedic medical procedure			
4.	First and review visits for interventions	First and revisits			
5.	Estimated renting building space in square feet	Floor measurements in square feet for 4 hospitals, and rent monthly for 12 months			
6.	Emoluments for occupational therapists	Number of occupational therapists at the 4 hospitals and monthly salary for 12 months			
7.	Emoluments support staff	Number of support staff at the 4 hospitals and monthly salary for 12 months			
8.	Staff-time for the medical superintendents/directors	Medical superintendents at the 4 hospitals for 12 months			
9.	Staff-time for chief nursing officers/directors	Number of chief nursing officers at the 4 hospitals and monthly staff-time for 12 months			
10.	Staff-time for health administrative officers/directors	Number of health administrative officers at the 4 hospitals and monthly staff-time for 12 months			
11.	Staff-time for orthopaedic surgeons	Number of orthopaedic surgeons at the 4 hospitals and monthly staff-time			
12.	Utilities for water and sewerage	Charges for water and sewerage monthly for 12 months			
13.	Utilities for electricity	Charges for electricity monthly for 12 months			
	Total ($)				

Appendix 6: Ethical approvals and considerations

The following attachments are included in this thesis: -

i. University of Nairobi and Kenyatta National Hospital, KNH-UoN Ethics and Research Committee Ref: KNH-ERC/A/44.
ii. National Commission for Science, Technology, and Innovation, Ref: NACOSTI/P/19/75586/28325.
iii. Office of the President, Ministry of Interior and Coordination of National Government, County Commissioner-Kiambu, Ref: No: ED.12(A)/1/VOL.II/107.
iv. Office of the President, Ministry of Interior and Coordination of National Government, State Department of Interior, Ref. No: CR/ADM/149/049/TY/47.
v. County Government of Kiambu County, Department Health Ref. No: Kiambu/HRDU/AUTHO/2019/03/06/AgotGN
vi. County Government of Kiambu, Department of Health, Thika Level 5 Hospital, Ref: NO. MOMS/TKA/VOL.III (728).
vii. County Government of Kiambu, Department of Health, Gatundu Level 5 Hospital, Ref: GTD/GEN/37/VOL.1/97.
viii. AIC Cure International Hospital-Kijabe.
ix. Turnitin Originality Report of 14% Similarity Index

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COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

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KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/44

7th February, 2019

Mr. George Nyadimo Agot
PhD Candidate
Reg.No.H80/52056/2017
School of Public Health
College of Health Sciences
University of Nairobi

Dear George

RESEARCH PROPOSAL – THE EPIDEMIOLOGY AND ECONOMIC BURDEN OF STRUCTURAL BIRTH DEFECTS IN KENYA: A CASE OF KIAMBU COUNTY (P701/09/2018)

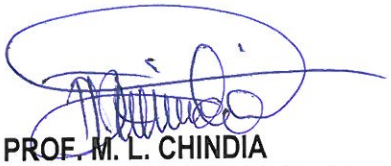
This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 7th February 2019 – 6th February 2020.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,



PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Director, School of Public Health, UON
Supervisors: Dr. Marshal M. Mweu, Prof. Joseph K. Wang'ombe, Prof. Mutuku A. Mwanthi

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Fax:+254-20-318245,318249
Email: dg@nacosti.go.ke
Website : www.nacosti.go.ke
When replying please quote

NACOSTI, Upper Kabete
Off Waiyaki Way
P.O. Box 30623-00100
NAIROBI-KENYA

Ref: No. **NACOSTI/P/19/75586/28325**

Date: **27th February, 2019**

George Nyadimo Agot
University of Nairobi
P.O. Box 30197-00100
NAIROBI.

RE: RESEARCH AUTHORIZATION

Following your application for authority to carry out research on ***"The epidemiology and economic burden of structural birth defects in Kenya: A case of Kiambu County"*** I am pleased to inform you that you have been authorized to undertake research in **Kiambu County** for the period ending **27th February, 2020.**

You are advised to report to **the County Commissioner, the County Director of Education and the County Director of Health Services, Kiambu County** before embarking on the research project.

Kindly note that, as an applicant who has been licensed under the Science, Technology and Innovation Act, 2013 to conduct research in Kenya, you shall deposit **a copy** of the final research report to the Commission within **one year** of completion. The soft copy of the same should be submitted through the Online Research Information System.

BONIFACE WANYAMA
FOR: DIRECTOR-GENERAL/CEO

Copy to:

The County Commissioner
Kiambu County.

OFFICE OF THE PRESIDENT

MINISTRY OF INTERIOR AND COORDINATION OF NATIONAL GOVERNMENT

STATE DEPARTMENT OF INTERIOR

Telegraphic Address: "CIVREG", NAIROBI
Telephone: Nairobi 020-2691109
Email: director@crd.go.ke
Fax: 2714989

CIVIL REGISTRATION SERVICES
Hass Plaza, Lower Hill Road
P.O. Box 49179 – 00100
NAIROBI

When Replying please quote

CR/ADM/149/049/TY/47

2nd August, 2019

Mr. George Nyadimo Agot
P O Box 1751 - 00200
NAIROBI

NUMBER OF LIVE BIRTHS BORN AND REGISTERED IN KIAMBU COUNTY IN 2014,2015,2016,2017 AND 2018

We are in receipt of your letter dated 17th July, 2019 in respect of the above matter.

We wish to confirm to you that the Department is willing to share information and data that it collects in the course of carrying out its mandate with persons or entities who intend to use the information for the common good of Kenyans.

Our statistics division based at the Head office will provide you with the information you need.

You are therefore asked to visit our statistics division in Hass Plaza and ask for Mr. Wambua Willy or Mr. Joseph Kirima. By copy of this letter the officers are requested to facilitate you with the data you require.

JANET W. MUCHERU, MKIM
DIRECTOR, CIVIL REGISTRATION SERVICES

Copy to: Willy Wambua
H/Statistics section

OFFICE OF THE PRESIDENT

MINISTRY OF INTERIOR AND CO-ORDINATION OF NATIONAL GOVERNMENT

COUNTY COMMISSIONER, KIAMBU

Telephone: 066-2022709
Fax: 066-2022644
E-mail: countycommkiambu@yahoo.com
When replying please quote

County Commissioner
Kiambu County
P.O. Box 32-00900
KIAMBU

Ref .No:**ED.12 (A) /1/VOL.II/107** **Date: 5th May, 2019**

George Nyadimo Agot
University of Nairobi
P.O.Box 30197- 00100
NAIROBI

RE: RESEARCH AUTHORIZATION

Reference is made to National Commission for Science, Technology and Innovation letter Ref No. **NACOSTI/P/19/75586/28325** dated **27th February , 2019.**

You have been authorized to conduct research on "***The epidemiology and economic burden of structural birth defects in kenya: A case of Kiambu County***" *The* research will be carried out in ***Kiambu County*** *for a period ending* **27th February , 2020.**

You are requested to share your findings with the County Education Office upon completion of your research.

Festus Kimeu
For: County Commissioner
KIAMBU COUNTY

Cc County Director of Education
KIAMBU COUNTY

National Commission for Science, Technology and Innovation
P.O. Box 30623-00100
NAIROBI

All Deputy County Commissioners
KIAMBU COUNTY

COUNTY GOVERNMENT OF KIAMBU
DEPARTMENT OF HEALTH SERVICES

All correspondence should be addressed to
HEAD HRDU - HEALTH DEPARTMENT
Email address: mndiritu@gmail.com
mkwasa@live.com
Mobile: 0721641516
0721974633

HEALTH RESEARCH AND DEVELOPMENT UNIT
P. O. BOX 2344 - 00900
KIAMBU

Ref. No: KIAMBU/HRDU/AUTHO/2019/03/06/Agot GN

Date: 06 Mar 2019

TO WHOM IT MAY CONCERN,

RE: CLEARANCE TO CONDUCT RESEARCH IN KIAMBU COUNTY

Kindly note that we have received a request by **Mr. George Nyadimo Agot** of **University Of Nairobi** to carry out research in Kiambu County, the research topic being on ***"The Epidemiology And Economic Burden Of Structural Birth Defects In Kenya: A Case Of Kiambu County"***.

We have duly inspected his documents and found that he has been cleared by **Kenyatta National Hospital-University Of Nairobi** until **06 Feb 2020**. He thus does not need any further clearance with another regulatory body in order to conduct research within the county of Kiambu.

However, it is incumbent upon the facility in which the research is being carried out to ensure that they are conversant with the remit of the study and operate in line with their institutional norms on conducting research. This note also accords him the duty to provide feedback on his research to the county at the conclusion of his research.

DR. M. NDIRITU NDIRANGU
COUNTY HEALTH RESEARCH DEVELOPMENT UNIT
KIAMBU COUNTY

COUNTY GOVERNMENT OF KIAMBU
DEPARTMENT OF HEALTH

Tel. Thika 067 21621/2 fax 21778
All correspondence should be addressed to
MED.SUPT.
When replying please quote

Ref: NO. MOMS/TKA/ VOL. III (728)

THIKA LEVEL 5 HOSPITAL
P.O. BOX 227
THIKA

Date: 11th April, 2019

APPROVAL TO CARRY OF RESEARCH

Principle investigator: GEORGE NYADIMO AGOT

RE: THE EPIDEMIOLOGY AND ECOMONIC BURDEN OF STRUCTURAL BIRTH DEFECTS IN KENYA A CASE OF KIAMBU COUNTY.

Following deliberations by Thika Level 5 hospital research committee, your proposal to carry out the above research at this facility has been approved. However, you will need to provide us with licence from NACOSTI before you can commence the data collection.

Take note that you are required to submit a copy of your research findings upon completion of the study to the hospital. It is also expected that the Ethical consideration and the research subjects confidentiality will be maintained as you have outlined in your proposal.

Any patient confidential information that you may access during your research should not be used without consent.

This letter is valid up to 30th September, 2019.

For any queries feel free to contact the committee chair through the Medical Superintendent's office. Thank you and all the best.

DR. J. WANGECHI
CHAIR TREC
THIKA LEVEL 5 HOSPITAL

COUNTY GOVERNMENT OF KIAMBU
DEPARTMENT OF HEALTH SERVICES
GATUNDU LEVEL 5 HOSPITAL

Telegram: "MEDICAL"Gatundu
Telephone: 0786 916 894
When replying please quote
Email Address:

GATUNDU LEVEL 5 HOSPITAL
P.O BOX 84 - 01030
GATUNDU
gatundul4h@gmail.com

Ref:GTD/GEN/37/VOL.1/97

7TH JUNE 2019

MR.GEORGE NYADIMO AGOT
ADM NO: H80/52056/2017

RE: AUTHORITY TO COLLECT DATA

Your application to conduct research on *"The epidemiology and economic burden of structural birth defects in Kenya: A case of Kiambu County"* in this institution has been granted.

During the entire period of your research, you will be reporting to the MO In charge Maternity, who will be the key Hospital Co-ordinator during the data collection. She will support you access any information that may be relevant for the successful undertaking of the research.

Finally, you are expected to adhere to all the regulations relating to confidentiality of patient information, ethics in research as well as all norms regarding conduct in a Public Health Institution.

Wishing you a successful research.

MEDICAL SUPERINTENDENT
Sign
07 JUN 2019
P. O. Box 84 - 01030
GATUNDU
GATUNDU LEVEL 5 HOSPITAL

KARIUKI J G
HEALTH ADMINISTRATIVE OFFICER
GATUNDU LEVEL 5 HOSPITAL

AIC CURE International Hospital
P.O.Box 52 – 00220 Kijabe, Kenya
Tel: 020 3246620, 0733 770 653
Email: info@curekenya.org

ACIH Institutional Research and Ethics Board (IRB) Ethics Approval Letter

17th June 2019

To: GEORGE NYADIMO AGOT, PHD , UON college of health sciences.

RE: Ethical Approval for Your Study

The Ethics and Research Board of AIC Cure Hospital has gone through your submitted request to undertake a non-invasive study titled **THE EPIDEMIOLOGY AND ECONOMIC BURDEN OF STRUCTURAL BIRTH DEFECTS IN KENYA: A CASE OF KIAMBU COUNTY",** and grants the approval for the study to be carried between July 2019 and February 2020.

Any variations to the protocol or dates of the study must have prior permission of the IRB. Any severe adverse effects on patients or bad outcomes must be reported within 24 hours to the IRB using the Incidence Reporting Forms. We expect at the end of collecting results you will alert IRB and that you will share the final study outcomes copy with us to facilitate transfer of knowledge and future decision-making. Should you abandon your study mid-way, kindly alert us in writing giving the reasons for such a decision.

We wish you well in your study. Feel free to seek further guidance from the IRB during your study.

Signed:

Dr.Jeff M. Mailu
Consultant Orthopedic and Arthroscopic Surgeon
IRB Chairperson, AIC Cure Hospital.

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