

**ASSESSMENT OF NEURAL TUBE DEFECTS IN TWO NORTHERN
NAMIBIA HOSPITALS: INCIDENCE, SEASONAL VARIATION, RISK
FACTORS AND PREVENTION STRATEGIES FOR FOLATE
SENSITIVE DEFECTS**

A THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR
THE
DEGREE OF

DOCTOR OF PHILOSOPHY IN MEDICINE-SURGERY

OF

THE UNIVERSITY OF NAMIBIA

BY

FILEMON AMAAMBO

STUDENT: 201512724

APRIL 2021

MAIN SUPERVISOR: PROF SHIRLEY HUDGSON

CO - SUPERVISORS: PROF CHRISTIAN HUNTER

PROF HONORÉ KABWEBWE MITONGA

ABSTRACT

Neural tube defects (NTDs) represent severe congenital abnormalities of the nervous system and are among significant abnormalities associated with a high mortality and morbidity rates. Studies reported that the incidence of NTDs varies worldwide, with the highest found in low-income countries. Most high-income countries have managed to document and the reduce incidence of NTDs through primary prevention strategies. However, inadequate documentation on NTDs is frequent in low and upper-middle income countries including Namibia. This study focused on assessing the incidence, seasonal variation, risk factors, and comparing the postpartum red blood cell folate in cases and controls in Onandjokwe and Oshakati hospitals in the Northern regions of Namibia over 12 months. The aims of the study were to identify evidence that NTDs constitute both a clinical and a societal problem. And, to propose locally adapted prevention strategies for folate –sensitive NTDs. The study objectives were to assess the incidence of NTDs, determine an association between the conception of NTD babies and seasonal variation (rainfall), identify related risk factors, and to compare postpartum maternal red blood cell folate in NTD cases and controls.

The study utilised a quantitative approach with a cross-sectional design to assess the incidence of NTDs and descriptive-statistical analysis to evaluate associated risk factors. A case-control design was used to compare postpartum maternal red blood cell folate between mothers of cases and controls. The study population was mothers who gave birth in the two hospitals during the period of 12 months. Non-random consecutive sampling was used to select participants - mothers with and without NTD babies - to minimise bias when studying rare conditions. Participants were informed, counselled and requested to sign consent forms. Questionnaires were

administered face to face to participants and blood samples were drawn to determine postpartum red blood cell folate. Data was analysed using Epi-info software.

The findings of the study were: a) the combined hospital neural tube defects incidence was 11 per 10000 births; b) there was a seasonal variation in the birth and conception of babies with NTDs, which could be associated with the seasonal rainfall pattern; c) the risk factors possibly related to NTDs were unemployment, low level of education, diet lacking fruits and vegetables, and low maternal red blood cell folate. Other risk factors, such as age, diabetes, HIV, obesity, smoking, alcohol, drugs, exposure to radiation, hyperthermia, family history, marriage, consanguinity, were not shown to play a significant role in NTD incidence. The study found hydranencephaly to be more common than spina bifida. The study proposed recommendations, future research areas and preventive interventional strategies for NTDs in the Northern regions. The study further underscored health education about NTDs, consumption of fruits and vegetables, folate supplementations + Vit B12 and food fortification for all childbearing women in a sustainable way.

TABLE OF CONTENTS	
ABSTRACT	i
LIST OF TABLES	vi
LIST OF FIGURES	vii
LIST OF ACRONYMS AND ABBREVIATIONS	ix
ACKNOWLEDGEMENTS	x
DEDICATION	xi
DECLARATION	xii
CHAPTERS OUTLINE	xiii
CHAPTER ONE: INTRODUCTION AND BACKGROUND OF THE STUDY	1
1.1. BACKGROUND OF THE STUDY	1
1.2. GEOGRAPHY OF NAMIBIA	2
1.3. STUDY CONTEXT	3
1.4. PROBLEM STATEMENT	7
1.5. AIM OF THE STUDY	8
1.6. OBJECTIVES OF THE STUDY	8
1.7. STUDY HYPOTHESES	10
1.8. SIGNIFICANCE OF THE STUDY	10
1.9. LIMITATION AND DELIMITATION OF THE STUDY	12
1.10. DEFINITIONS OF CONCEPTS	12
1.11. SUMMARY	13
CHAPTER TWO: LITERATURE REVIEW	14
2.1. INTRODUCTION	14
2.1.1. What are NTDs?	15
2.1.2. Types of NTDs	16
2.1.3. Aetiology and Mechanisms how NTDs occur	17
2.2. EPIDEMIOLOGY AND MANAGEMENT OF NTDs	18
2.2.1. Incidence	19
2.2.2. The burden	24
2.2.3. Risk factors	25
2.2.4. Diagnosis	26
2.2.5. Prognosis	27
2.2.6. Operative Treatment	30
2.2.7. Prevention	31
2.3. KEY FINDINGS AND CRITICAL REFLECTIONS	33
2.4. SUMMARY	36
CHAPTER THREE: RESEARCH METHODOLOGY	37

3.1. INTRODUCTION	37
3.2. RESEARCH DESIGN AND METHOD	37
3.2.1. Variables	39
3.3. POPULATION	40
3.3.1. Inclusion Criteria	41
3.3.2. Exclusion Criteria	43
3.4. SAMPLING	44
3.4.1 Sampling procedure	45
3.4.2. Sample size	46
3.5. DATA COLLECTION INSTRUMENTS AND PROCEDURE	48
3.5.1. Questionnaire	49
3.5.2. Questionnaire development	50
3.5.3. Piloting questionnaire	50
3.5.4. Pilot study outcomes	51
3.5.5. Administration of the questionnaire	51
3.5.6. Blood Samples	52
3.5.7. Maternity records review	53
3.6. DATA COLLECTION PROCEDURE	53
3.7. VALIDITY AND RELIABILITY	54
3.8. DATA ANALYSIS	56
3.9. RESEARCH ETHICAL CONSIDERATIONS	57
3.10. SUMMARY	59
CHAPTER FOUR: RESULTS	60
4.1. INTRODUCTION	60
4.2. DETERMINATION OF INCIDENCE OF NTDs PER 10000 BIRTHS	60
4.3. SEASONAL VARIATION IN BIRTH OF BABIES WITH NTDs	63
4.4. MEAN POSTPARTUM MATERNAL RED BLOOD CELL FOLATE IN CASES AND CONTROLS	66
4.5. OTHER RISK FACTORS	69
4.6. SUMMARY	86
CHAPTER FIVE: DISCUSSION	87
5.1. INTRODUCTION	87
5.2. INCIDENCE OF NTDs PER 10000 BIRTHS	89
5.3. SEASONAL VARIATION IN BIRTH OF BABIES WITH NTDs	94
5.4. MEAN POSTPARTUM MATERNAL RED BLOOD CELL FOLATE IN CASES AND CONTROLS	96
5.5. OTHER RISK FACTORS	104
5.6. SUMMARY	113

CHAPTER SIX: CONCLUSIONS, RECOMMENDATIONS AND INTERVENTIONAL STRATEGIES	114
6.1. INTRODUCTION	114
6.2. CONCLUSIONS	114
6.3. RECOMMENDATIONS	117
6.4. INTERVENTION STRATEGIES AND APPROACHES	119
Stage 1: NTDs Education and Advocacy	120
Stage 2: Folate Supplementation	121
Stage 3: Food Fortification	122
Stage 4: Gardening	124
6.5. LIMITATIONS	126
6.6. SUMMARY	127
APPENDIX	145
Annexure A: Permission Letter from UNAM	145
Annexure B: Ethical Clearance Certificate from UNAM	146
Annexure C: Permission Letter from Permanent Secretary, Ministry of Health and Social Services	147
Annexure D: Request for Permission to Medical Superintendents	149
Annexure E: Request for Permission to the Permanent Secretary, MOHSS	151
Annexure F: Informed Consent – English Version	153
Annexure G: Informed Consent – Oshiwambo Version	154
Annexure H: Information to Participants – English Version	155
Annexure I: Information to Participants – Oshiwambo Version	158
Annexure J: Instructions for Interviewers	161
Annexure K: Questionnaire Guide	163
Annexure L: Questionnaire Guide – ANC Record	166

LIST OF TABLES

Table 1: Regional meta-analysis of overall birth prevalence of NTDs (per 10000 births)	20
Table 2: Summarized NTD incidence in some African Countries.....	23
Table 3: Categories of neural tube defects, their features and sequelae	28
Table 4: Estimated congenital abnormality deaths and numbers of neonatal deaths due to NTDs for 2005 by the WHO region (low-income/high neonatal mortality countries) - Sub-Saharan Africa.....	29
Table 5: Selection criteria for inclusion for the assessment of incidence of NTDs ..	41
Table 6: Selection criteria for exclusion for the assessment of incidence of NTDs .	44
Table 7: Sample Selected from the Population.	47
Table 8: The distribution of type of NTDs per hospital	61
Table 9: The distribution of cases of neural tube defects by region	63
Table 10: Gravidity and parity	73
Table 11: Percentage anaemia.....	85
Table 12: Radiation exposure, consanguinity, marriage, drugs and smoking.....	85
Table 13: Cost benefit ratios achieved in different countries	92

LIST OF FIGURES

Figure 1. The map presents Namibian regions.....	4
Figure 2. Relationship between periconceptional red blood cell folate and neural tube defects (Crider et al., (2014).	6
Figure 3. Some of the typical NTDs	17
Figure 4. NTD Cases per Hospital	62
Figure 5. Types of NTDs	62
Figure 6. Seasonal variation, conceptions and births of NTD babies in relation to month and rainfall.	64
Figure 7. Seasonal variations in births	66
Figure 8. Mean postpartum red blood cell folate	67
Figure 9. Values of red blood folate among cases and controls.....	68
Figure 10. Maternal postpartum red blood cell folate value per type of NTD.....	69
Figure 11. Work Status (OR = 0.6750; CI = 0.1177 – 3.8726; P VALUE = 1.00)	70
Figure 12. Education level (OR = 1.00; CI = 0.1891 – 5.2893; P VALUE = 0.66)	71
Figure 13. Knowledge of NTDs (Cases 50% know, Controls 54% know, No difference.)	72
Figure 14. Diabetes and neural defects	74
Figure 15. Distribution of fruit and vegetable diet among cases and control	75
Figure 16. Alcohol consumption during pregnancy.....	76
Figure 17. Human Immune Deficiency Virus (HIV) Status	77
Figure 18. Hyperthermia / Extreme temperature	78
Figure 19. Age distribution for the cases and controls.....	79

Figure 20. Body Mass Index (BMI) of mothers with and without neural tube defect (NTD) babies.....	80
Figure 21. BMI can be calculated as shown in the chart above.	81
Figure 22. Family history	82
Figure 23. Haemoglobin (Hb)	83
Figure 24. Mean haemoglobin	84
Figure 25. Total Serum Folate in circulation during pregnancy and lactation.....	97

LIST OF ACRONYMS AND ABBREVIATIONS

ANC	Ante Natal Care
BMI	Body Mass Index
CSF	Cerebrospinal fluid
CT	Computerised Tomography Scan
EDTA	Ethylenediaminetetraacetic Acid
EPI INFO	Epidemiological Information Software
EU	European Union
FAO	Food and Agriculture Organisation
FFI	Food Fortification Initiative
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
IRDiRC	International Rare Disease Research Consortium
MDGs	Millennium Development Goals
MoHSS	Ministry of Health and Social Services
MTHFR	Methylenetetrahydrofolate reductase
NIP	Namibia Institute of Pathology
NTD	Neural Tube Defect
NTDs	Neural Tube Defects
NSA	Namibia Statistical Agency

ACKNOWLEDGEMENTS

This study was conceptualized and conducted during one of the most challenging phases of my life. For that reason, I remain most grateful to God Almighty who made it possible to complete it through his holistic hand.

The inspiring support of my supervisors: Professors Shirley Hodgson, Christian Hunter and Honore K. Mitonga is profoundly acknowledged. The study opportunity granted by the management of the University of Namibia and motivating contributions of members of the Faculty of Health Sciences are highly appreciated.

I am indebted to the management of the Ministry of Health and Social Services for permission to conduct research in the two hospitals, Oshakati and Onandjokwe. I would like to extend gratitude for profound support received from the participants and staff of the two hospitals, especially the Maternity and Neonatal Units.

I wish to express great appreciation for assistance and support received from Drs S. Mtombeni, K. Kalambayi, and T. Munyoka, interns and nursing staff during the data collection phases. The contributions from Dr. S. Mtombeni, Mr. S. Nghoshi and Mr. M. Naukushu, during the data analysis phase, deserve individual credit. The assistance of Ms. J. Namene during the finalisation of the dissertation is profoundly appreciated.

I want to acknowledge support from international researchers, namely Prof Hanna Blencowe, for valuable comments and the provision of additional literature relevant to the study.

Lastly, I wish to express full appreciation for the support and encouragement received from my family throughout the study, without which it would have been impossible to complete it.

Thank you so much!

DEDICATION

The study is dedicated to the children of Namibia. It also represents a bold step towards the realisation and promotion of the well-being of the unborn child, including the embryo, and to spare it from death in-utero. Although not all possible risk factors for NTDs can be minimised, every effort is required to identify and reduce common risk factors linked to defects associated with major challenges to individuals, families and broader society. Many countries of the world have already developed and implemented programmes to ensure good health for their children. The children of Namibia should not be left behind.

DECLARATION

I, Filemon Amaambo, hereby declare that this study is my work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

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Name of student	Signature	Date

CHAPTERS OUTLINE

The chapters in this study are delineated as follows. **Chapter 1** presented the introduction and background of the study, study context, the problem statement, aims and objectives of the study, research questions, hypothesis, significance, delimitation and limitation of the study, definition of concept and the summary. **Chapter 2** offered the review of the relevant literature. **Chapter 3** offered research design, and methodology. **Chapter 4** presented results of the study; **Chapter 5** consists of discussions, in which the interpretation of the results is presented. **Chapter 6** presented the conclusions, recommendations and interventional strategies to mitigate the high incidence of neural tube defects in the Northern regions of Namibia.

CHAPTER ONE: INTRODUCTION AND BACKGROUND OF THE STUDY

1.1. BACKGROUND OF THE STUDY

This chapter provided the introduction and background to understand the concept of NTDs and gave a broad description of Namibia in terms of its geography, regions, population, and farming as well as household food security. Namibia is situated in the Southwestern part of Africa, and is 825 214 square kilometers in size. The country shares its borders with South Africa, Zimbabwe, Botswana, Zambia, Angola and the South Atlantic Ocean to the west. It has a population of 2 113 077 with an annual growth rate of 1.4% (NSA, 2014). The country has relatively good roads and communication infrastructure.

The 2011 census indicated that, Namibia has 2.1 million with 57% of the population lives in communal areas, while 43% lives in commercial urban centers (NSA, 2013). Namibia is a vast country with a small and sparse population. A population of 67% lives in rural areas, with the majority in the northern belt of the country. According to the Namibia Food and Agriculture Organisation (FAO), the country has low average rainfall, high levels of poverty, food insecurity, low education level, lack of appropriate farming methods and a high unemployment rate (FAO, 2005).

Correspondingly, a survey conducted by the Ministry of Health and Social Services (MoHSS) in 1992 documented the high prevalence of iodine deficiency ‘goitre’ (a micronutrient) in school children from Northern regions of Namibia (Nations, 2003) and (Health & Services, 2005). The above finding could be associated with deficiencies in other micronutrients such as folic acid.

1.2. GEOGRAPHY OF NAMIBIA

Namibia is a country of natural geographic contrasts with a desert along the coast, bush veld in the north west, a mountainous central plateau and a semi-desert in the south east. Average rainfall is around 300-400 mm per year in the north eastern regions and less than 50 mm per year in the south and along the coast. Heavy winds are common in the southwestern regions. Perennial rivers are found along the northern, eastern and southern borders. No perennial rivers traverse the country. Temperatures may reach 40°C in north eastern regions, while 0°C temperatures may occur in the southern and central regions. Mining and fishing are mostly carried out in the southern regions and along the coast. Most of the land in Namibia is privately owned, leaving 70% of the population living on 35% of the land (Melber, 2019).

According to Awala et al. (2019), the main sources of livelihood in Northeast regions is mainly rainfall fed farming activities, such as millet and maize, as well as livestock farming. The rainy season in north eastern regions is from November to April when 97% of rain falls. Floods sometimes come from Angola in the North. The dry season is usually from May to October when only 3% of rain falls (9-18mm). Drought spells are sometimes experienced.

Angula et al. (2016), stated that, variable rainfall, floods and drought spells aggravate household food security, leading to malnutrition and outbreak of diseases. The main sources of livelihood were listed in order of significance as follows for north central Namibia: crop farming, livestock farming, social grants and lastly formal employment.

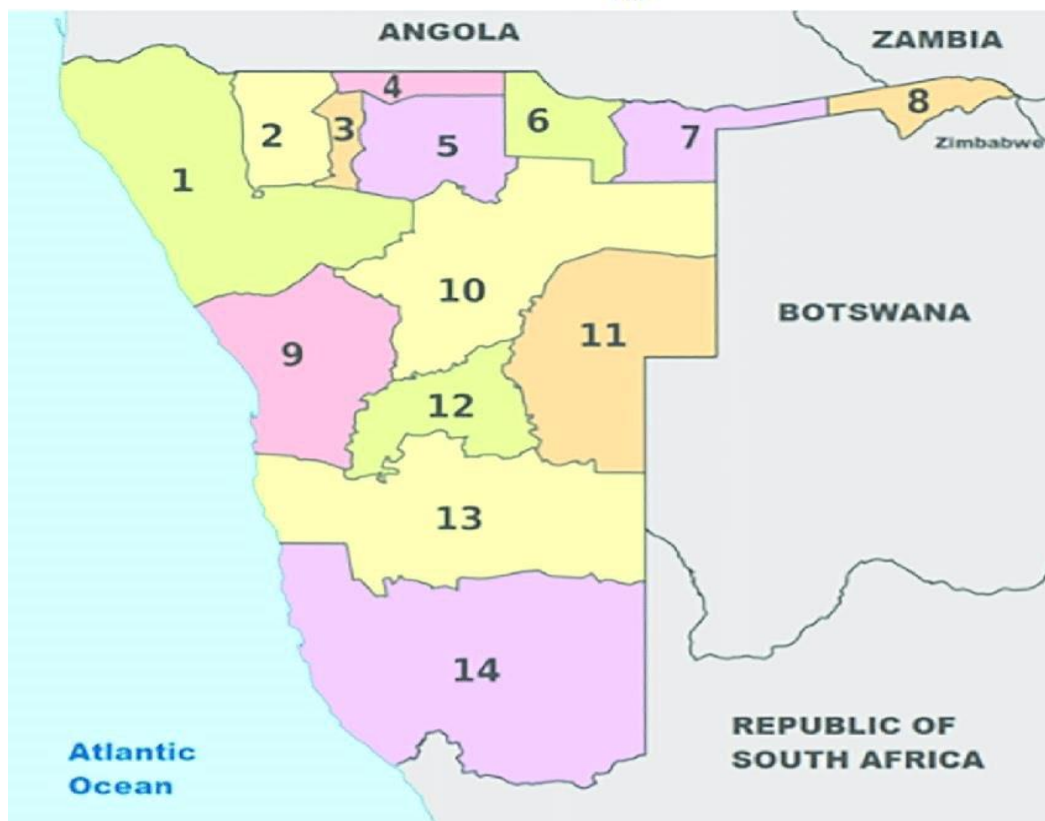
Melber (2019) further stated that, although the majority of the Namibian population still lives in the rural areas despite high rural-urban migration among the youth, many women and children continue to experience socio-economic hardship in terms of - access to good education, employment opportunities, shelter, food security and limited health services beyond primary care clinics, water supply and sanitation. There is a close relationship between social conditions, nutrition and health.

1.3. STUDY CONTEXT

Onandjokwe hospital with 500 beds and Oshakati hospital with 800 beds are both referral public regional hospitals situated in Oshikoto and Oshana region respectively and 40 km apart. They receive referrals from clinics and districts hospitals. Each hospital conducts over 7000 deliveries per year, and each is served by consultants in obstetrics, paediatrics, and surgery supported by interns, medical officers and nurses.

Brain ultrasound can be performed in both hospitals, while computerized tomography scan (CT scan) is only available in Oshakati hospital with the consultant radiologist in charge. The researcher was a consultant surgeon to both hospitals for more than 30 years and experienced NTD related challenges over that time. Neonatal units are extensions of maternity wards in both hospitals. The population served is largely rural based. Figure 1 below indicates the regions in which the study areas are situated. Onandjokwe hospital is situated in Oshikoto region, while Oshakati hospital is in Oshana region.

Namibian Regions



- | | |
|-----------------|------------------|
| 1. Kunene | 9. Erongo |
| 2. Omusati | 10. Otjozondjupa |
| 3. Oshana | 11. Omaheke |
| 4. Ohangwena | 12. Khomas |
| 5. Oshikoto | 13. Hardap |
| 6. Kavango West | 14. Karas |
| 7. Kavango East | |
| 8. Zambezi | |

Figure 1. The map presents Namibian regions

(Source: https://en.wikipedia.org/wiki/Regions_of_Namibia).

Figure 1 shows the three regions in Northern Namibia that were of interest in this study with corresponding populations, namely; Oshana (3) 174 900, Ohangwena (4) 245 100 and Oshikoto (5) 181 600. Comprehensive health services are provided by the two referral state hospitals in the Northern regions of Namibia. These hospitals were studied to get a better depiction of the incidence of NTDs in Northern Namibia.

Neural tube defects (NTDs) represent a group of severe congenital malformations of the central nervous system. They result from the failure of neural tube closure during early embryonic life (Bassuk & Kibar, 2009). NTDs include malformations of the spinal cord and brain. Environmental factors possibly implicated in increasing the risk for NTDs in previous studies include geography (such as rainfall), epidemic trends, socio-economic class, maternal age, maternal diet, maternal diabetes maternal obesity, and drug exposure mainly to antiepileptic drugs (Bassuk & Kibar, 2009). In general, some gaps in information have been observed. Folic acid deficiency during the periconceptual period is an important risk factor for NTDs, and the mechanisms involved have been studied. Blom, Shaw, den Heijer, & Finnell, (2006) proposed a methylation hypothesis. A systematic review and meta-analysis, indicates that data from low-income countries is under-represented, raising questions as to what extent such findings on this topic can be generalized (Mustafa, 2014).

According to Crider et al. (2014), there is an inverse relationship between periconceptual red blood cell folate concentration and the incidence of NTDs, as presented in figure 2.

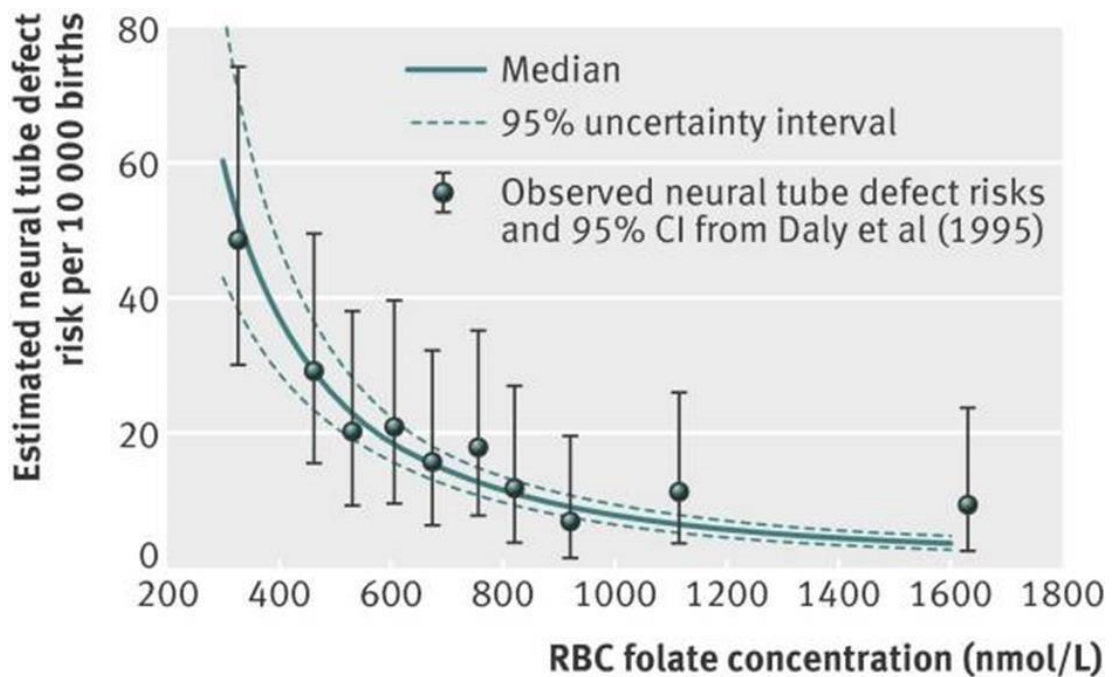


Figure 2. Relationship between periconceptional red blood cell folate and neural tube defects (Crider et al., (2014).

In Namibia, the incidence of NTDs per 10000 births has not yet been documented. In addition, Namibia has not yet documented the maternal red cell folate in order to benchmark with the reported cut-off level of 906 nmol/l at 28 days gestation above, which few folate-sensitive neural tube defects can be expected (Crider, 2014). According to the 2011 census, about 2.1 million people live in Namibia, 57% in rural areas and 43% in urban areas and 52% are women with a fertility rate of 3.6 children. Namibia is classified as an upper middle class income country (World Bank Group, 2014). The 2014 hospital monthly statistics report revealed that Onandjokwe and Oshakati hospitals each conducted over 6000 deliveries annually. Very often, some babies are born with NTD of varying types and severity.

Namibia appears to have a high burden of babies born with NTDs in Onandjokwe and Oshakati hospitals, as observed by the researcher during surgical consultations. However, the burden has not been scientifically quantified and documented. Many

babies die early, while some survive because surgeons have been able to perform palliative surgery. Therefore, there was a need for a cross-sectional incidence study to document the incidence of NTDs, and to compare risk factors including postpartum maternal red cell folate using case-control methodology.

1.4. PROBLEM STATEMENT

NTDs pose major clinical, social and economic challenges globally. High-income countries managed to achieve milestones in terms of understanding the aetiology and mechanisms of development, early diagnoses, improved treatment, prevention and reduction in incidences and socio-economic burdens. Folic Acid deficiency prior to and in early pregnancy is one well-recognized risk factor of NTDs (Mustafa, 2014). There are also other genetic and environmental risk factors that are a subject of ongoing research. Many challenges exist in terms of ensuring that all pregnant women receive adequate folic acid in the periconception period (Wallingford et al, 2013). Available prevention strategies are mainly based on either timely folate supplementation or food fortification for folate sensitive NTDs.

In Namibia, babies with NTDs are born in hospitals, but the accurate statistics are not available. There is no documentation of county or hospital incidence per 10 000 births. The risk factors likely to contribute to births of NTD babies have not been assessed and documented, locally. The country has neither a policy nor a structured program to prevent folate sensitive NTDs.

The current use of tablets containing folic acid given to pregnant women during antenatal care (ANC) is targeting correction of macrocytic anaemia before delivery

rather than primary prevention of NTDs. The clinical, social and financial challenges continue to be observed in the hospitals and community, based on publications in local media. The need for a baseline study focusing on NTD in the local context is therefore recognised as an initial step to contribute to the understanding of the local situation and to identify ‘leads’ to guide future focused and in-depth research. The next section defines the preliminary as well as the ultimate aims of the study. This information is crucially needed in order to contribute to future public policy formulation on NTDs in the country.

1.5. AIM OF THE STUDY

The aim of the study is divided into categories, namely the preliminary general objectives and the ultimate specific objectives. The preliminary aim is to identify evidence that NTDs constitute both a clinical and a societal problem in Northern Namibia. The ultimate aim is to develop a strategy to prevent folate-sensitive NTDs in the northern regions of Namibia.

1.6. OBJECTIVES OF THE STUDY

To achieve the above aim, specific objectives were presented based on two phases:

Phase 1: Situational analysis – these are primary objectives to document the current situation about NTDs in Northern Namibia, namely:

- To determine the incidence of NTDs per 10 000 births over 12 months;
- To determine whether a seasonal variation (by month) exists in the birth of babies with NTDs;
- To compare mean postpartum maternal red blood cell folate between cases and controls

- To identify the possible risk factors associated with NTDs babies.

After the above-mentioned four objectives were addressed as a baseline, the ultimate objective is:

- To recommend prevention strategies for folate sensitive NTDs.

Phase 2: Formulation of the interventional strategy – these secondary objectives described measures to mitigate the incidence of neural tube defects identified in the study in Northern Namibia.

- To present recommendations to respond to the challenge of NTDs;
- To identify prospective research areas to address knowledge gaps emanating from the study results;
- To develop locally adapted intervention strategies for community health education and prevention of folate sensitive NTDs in Northern Namibia.

Research questions related to Northern Namibia:

- What is the incidence of neural tube defects per 10 000 births over 12 months' periods?
- Are there seasonal variations in the birth of babies with NTDs?
- How do the means of postpartum maternal red blood cell folate compare between cases and controls?
- What are the possible risk factors associated with the NTD babies?
- Which prevention strategies can be recommended for folate sensitive NTDs?

By answering these questions, the researcher will be able to establish the incidence of NTDs in Namibia and determine whether reduced levels of folic acid has a probable association to NTDs.

1.7. STUDY HYPOTHESES

- Ho, 1 (Null hypothesis 1)

There is no seasonal variation in the birth of neural tube defects babies.

- Ho. 2 (Null hypothesis 2)

There is no difference in mean postpartum maternal red blood cell folate for mothers of babies with and without neural tube defects.

1.8. SIGNIFICANCE OF THE STUDY

NTDs and their related challenges occur globally, leading to many high-income countries to undertake research to understand and document the magnitude and the risk factors followed by the intervention to address the problem (Mustafa, 2014). After intervention, it was realised that the benefits of prevention were more than the cost of treatment, which is never curative. The low-income countries on the other hand have not done much research and documentation of the magnitude, risk factors and prevention strategies.

In Namibian hospitals, many NTD babies are born, but the medical and surgical treatments remain suboptimal and palliative. Many desperate mothers continue to appeal for assistance through local media for resources to improve treatment (Kangootui, 2016) & (Kahiurika, 2019). This concern has prompted the researcher to recognise the need for baseline research into the problem of NTDs, which should

include documenting the incidence, assessing the locally relevant risk factors, diagnosis and treatment and eventually contributing to prevention strategy.

The following arguments are put forward in support of the local study in Northern Namibia:

There is a need to measure red blood cell folate at the population level, to document the red blood cell folate status of women during the periconceptional period, and to assess perinatal maternal red blood cell folate as an index of folate status during pregnancy. To date, there are no studies documenting the incidence of NTDs per 10 000 births in Namibia.

Furthermore, future primary prevention strategies might help to reduce the overall infant mortality rate in Namibia as part of sustainable development goals (SDGs). There is a need to reduce the burden of disability in Namibia by reducing the number of babies born with preventable NTDs. There is a need to improve capacity to monitor the occurrence of NTDs, and the cost savings from preventing the birth of babies affected by neural tube defects should be estimated, to allow an estimate to be made of the cost benefits of prevention strategies. The findings of this study highlighted the factors likely to be associated with NTDs in Namibia. This will therefore inform policy makers in planning strategies to reduce the incidence of these defects.

Namibia needs to prepare intervention strategies to prevent folate-sensitive NTDs and deal morally, clinically and socio-economically with those that could not be prevented. Surviving babies with NTDs often face life-long disabilities and pose many challenges to families, communities and the state at large. A successful

conclusion of this study has immense potential to guide the public health policy on prevention and documentation of the magnitude of the problem.

1.9. LIMITATION AND DELIMITATION OF THE STUDY

Since this study was conducted in two hospitals and there are many other regions in Namibia, which have specific local profile characteristics, the generalization of the findings to the whole country will need some adaptation to the contexts of the specific regions. This study is also limited because it excludes women giving birth either at private facilities or at home. The study was carried out during the following period: formally starting on 1 September 2016 and conducted up to the 31 August 2017 in Onandjokwe and Oshakati hospitals located in Oshikoto and Oshana regions respectively.

1.10. DEFINITIONS OF CONCEPTS

1.7.1 **Folic acid** – a B vitamin that is an essential factor in nucleic acid synthesis.

Lack of folic acid or folate during pregnancy can lead to neural tube defects in babies as defined by Webster's New World Medical Dictionary (Shiel, 2009)

1.7.2 **Incidence** – the frequency with which something, such as a disease or trait, appears in a particular population or area. It also refers to the number of new cases that develop in a given period (Shiel, 2009).

1.7.3 **Neural tube defect** – is a major birth defect caused by abnormal development of the neural tube, the structure that gives rise to the central nervous system (Shiel, 2009).

1.7.4 **Prevalence** – The proportion of individuals in a population having a disease or characteristics. It is a statistical concept that refers to the number of cases of a disease present in a particular population at a given time (Shiel, 2009).

1.11. SUMMARY

This chapter provided the background and the local study context and reflected on birth defects in Namibia and other countries. A description of challenges associated with incidence of NTDs in two state hospitals in Northern Namibia was provided in the problem statement. The aims, objectives, research questions and hypothesis were formulated. The significance of the study, limitations and delimitations together with definitions were highlighted. Chapter 2 proceeds with the review of related literature and documents on the subject of NTDs both globally and locally.

CHAPTER TWO: LITERATURE REVIEW

2.1. INTRODUCTION

The previous chapter presented the background and outline of the study. The aim, objectives and context in which the study was based were discussed. This chapter intends to review related literature and studies to obtain a deeper understanding of the foundation of key concepts and get knowledge on the subject of neural tube defects (NTD) both globally and locally. The introduction, epidemiology and management of NTDs, key findings as well as the critical reflections have been reviewed and lastly a summary of the chapter. The sources consulted include randomised controlled trials, systematic reviews and single studies. Van der Walt & Van Rensburg, (2012) defined literature review as an approach of finding, reading, understanding and forming conclusions about the published research and theory and presenting it in an organized manner. Therefore, the chapter documents what is already known on the subject of NTDs and identifies knowledge gaps that may exist on the subject in general and for Namibia in particular.

The review enabled the researcher to identify evidence to guide intervention strategies to reduce the incidence and burdens of NTDs in Namibia. This is to enhance the probability that the study generates novel ideas and knowledge on the topic of NTDs. Scholarly work based on controlled clinical trials, systematic reviews and case control studies was reviewed for strong evidence. Some of the references were classic since this was a unique study. Such references were cited to emphasize firstly, the importance of the role of balance diet in the prevention of diseases and malformation as a natural phenomenon and secondly, to point out that it took a long time for

scientific knowledge to be documented and eventually applied in developing countries such as Namibia.

2.1.1. What are NTDs?

NTDs involve variable degrees of mal-development of neuropore, adjacent bone, and other structures derived from ectoderm and mesoderm during early embryogenesis (Kaufman, 2004). Neural tube defects (NTDs) constitute one of the most common malformations of a human structure with a major public health burden affecting 5-20/10000 pregnancies worldwide (Salih & Murshid, 2014a). They remain a preventable cause of stillbirth, neonatal and infant death, or significant lifelong disabilities. Mildly affected babies may survive to adulthood without disabilities (spina bifida occulta). The underlying pathology is the consequence of a defect in the neurulation process very early in pregnancy, between 21 and 28 days after conception, leading to failure of the neural folds to fuse in the midline and form the neural tube (Salih & Murshid, 2014a). Secondary abnormal development of the mesoderm, which is responsible for forming the skeletal and muscular structures that cover the underlying neural structures, follows. This results in dysraphism, which indicates persistent continuity between the posterior neural ectoderm and cutaneous ectoderm. This was based on embryological considerations and the presence or absence of exposed neural tissue.

Complex dysraphic states are disorders characterized by aberrant formation or integration of the notochord, which is the inductor of the neural ectoderm and constitutes the foundation of the axial skeleton. (Salih & Murshid, 2014a). These include caudal regression syndrome, which ranges from agenesis of the coccyx to absence of the sacral, lumbar, and lower thoracic vertebrae to sirenomelia (or

mermaid syndrome), characterized by fusion of the lower limbs and other major organ malformations (Seidahmed, 2014). Complex dysraphic states due to aberrant integration of the notochord include split cord malformation (SCM) or diastematomyelia: a congenital spinal anomaly in which there is longitudinal splitting of the spinal cord (Elgamal et al., 2014).

Causes of NTDs are multifactorial and defects in several different genes can contribute to this disease's genetic basis (Salih & Murshid, 2014a). However, inheritance is commonly polygenic, with strong influence environmental factors, which affect genes that regulate folate one-carbon metabolism and planar cell polarity. In Saudi Arabia and several other countries, consanguinity was suggested to contribute to the high incidence of NTDs (Seidahmed, 2014). A higher proportion (20%) of syndromic NTDs, often associated with chromosomal anomalies, has also been documented compared with less than 10% elsewhere (Seidahmed, 2014).

2.1.2. Types of NTDs

According to Salih et al. (2014b), neural tube defects can be categorized as cranial and spinal, open or closed. The cranial type of neural tube defects can be outlined as follows; anencephaly, hydranencephaly, iniencephaly, encephalocele, meningoencephalocele, and cranioarachnoid. Types of spinal tube defects are classified as follows; meningocele, meningomyelocele and spina bifida occulta. Any type of neural tube defect may be associated with some other congenital malformation unrelated to the nervous system. Furthermore, Salih et al. (2014b) classified NTDs as open or closed types. Cranial dysraphism/malformation (failure of cranial neural tube closure) includes anencephaly and encephaloceles, whereas spinal dysraphism

(due to failure of caudal neuropore closure) is divided into open spinal dysraphisms (myelomeningocele, myelocele, hemimyocele, and hemimyelomeningocele) and closed spinal dysraphisms. The latter can be associated with subcutaneous mass and includes lipomas with dural defect and meningocele. Copp et al. (2013) reported NTD types as pre- closure disorders including anencephaly, open spina bifida and cranioarachnischisis, while post-closure disorders include encephalocele, meningocele and iniencephaly.

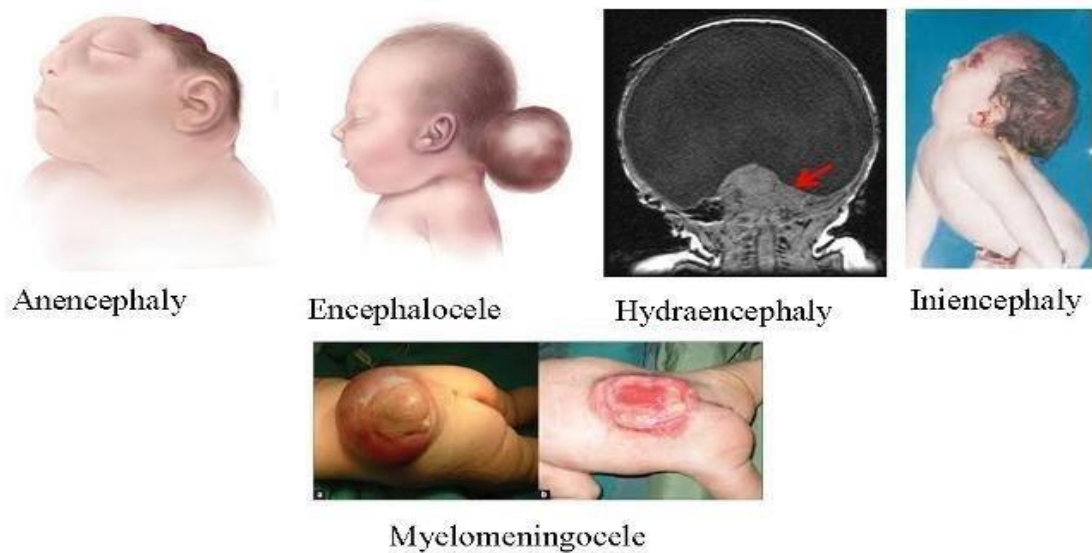


Figure 3. Some of the typical NTDs

Source: <https://neoreviews.aappublications.org/content/13/4/e233>

2.1.3. Aetiology and Mechanisms how NTDs occur

The aetiology of NTDs is multifactorial, involving complex interactions of genetic, biological and environmental factors (Wallingford et al., 2013). Furthermore, embryological changes were summarised from ectodermal cell proliferation, neural plate formation, neural crests and neural folds' formation, elongation and closure to

form a neural tube. The neural tube should normally be closed, but may remain open if the embryological processes become defective. The neural tube closure usually manifest complex, autonomous and region specific changes in cell behaviour resulting in thickening, elevation, medial motion, bending, narrowing and eventual epithelial fusion (Wallingford et al., 2013). They further state that the closure process is genetically regulated, discontinuous and initiated at multiple sites leading to sub-types of neural tube defects. The disruption of normal cilia function and cell-to-cell signaling (planar cell polarity) contributes to defect formation.

Much earlier, Scott et al. (1994) proposed a methylation theory to explain the mechanisms by which neural tube defects occur. It refers to the biochemical reactions of supplying methyl groups or their utilization, resulting in interrupted DNA synthesis or failure of neural tube closure. Folic acid plays an important role in the methylation reactions. Copp et al. (2013) highlighted the importance of genetic regulation by methylenetetrahydrofolate reductase (MTHFR) in the NTDs closure.

2.2. EPIDEMIOLOGY AND MANAGEMENT OF NTDs

According to Brink et al. (2012), epidemiology involves gathering information on health and illness in the human population, including the contributing factors, and prevention measures. Therefore, this section presents the conditions under which the neural tube defects occur in terms of incidence, burdens, risk factors, diagnosis, treatment, prognosis and prevention, in order to study the problem of NTDs in Northern Namibia.

2.2.1. Incidence

The incidence of neural tube defects (NTDs) may vary from country to country and from region to region within the same country. Brinks and Landwehr (2015) define incidence as occurrence of primarily new cases in a specific health-related state during a period, while prevalence looks at pre-existing cases and the proportion of subjects in the population at a given time. This study, however, focused on the incidence of NTD over 12 months in Northern Namibia. NTDs are a global concern, although over the years the high-income countries through preventive interventions have managed to reduce their incidence to lower levels. According to Crider (2014), an incidence of 8/10000 births or more warrants urgent intervention to reduce it. In addition, a study by Polšek, Sidhu & Lo (2014), revealed that the incidence of neural tube defects is higher in low-income countries as compared to high-income countries.

A study conducted by Blencowe et al. (2018), on “Worldwide NTDs: estimates for 2015” outlined the regional prevalence of neural tube defects. Table 1 below presented data from one country (South Africa) with folic acid fortification, while six studies were from countries without folic acid fortification.

Table 1: Regional meta-analysis of overall birth prevalence of NTDs (per 10000 births)

Source: (Blencowe et al., 2018)

Region	Number of Studies	NTD prevalence per 10000 births.
Australasia	1	12.10
Latin America and the Caribbean: with folic acid fortification	12	7.78
Latin America and the Caribbean: without folic acid fortification	1	22.89
Eastern Europe and Central Asia	6	9.92
Sub-Saharan Africa: with folic acid fortification	1	9.95
Sub-Saharan Africa: without folic acid fortification	6	15.27
East Asia	9	19.44
Northern Africa and Western Asia	9	17.45
Europe	17	8.63
Southeast Asia	2	6.76
North America	NA	
Southern Asia	11	31.96

Table 2 indicates that with folic acid fortification, the prevalence of NTDs could be reduced by 30% or more. In a different study in South Africa (SA), Sayed et al. (2008) demonstrated the benefit of fortification on NTDs by comparing pre-fortification figures (January 2003 to June 2004) with post-fortification figures (October 2004 to June 2005).

They found that the overall rate of NTD births dropped from 112 to 45, (1.41/1000 to 0.98/1000) while mortality rate dropped from 204 to 43, (0.419/1000 to 0.143/1000) respectively over the specified periods. Similar comparisons were not found from other Sub-Sahara Africa countries, which shows that the prevalence of NTDs in low and middle-income countries is not fully documented. This is because of the non-availability of surveillance registers in many countries of lower and middle-income countries (Zaganjor et al. 2016). Furthermore, Zaganjor et al., (2016) state that the lowest reporting of surveillance registers of 17% came from the African region, while the highest of 57% came from the East Mediterranean countries. Other regions reported 0% surveillance systems existed in low-income countries, while 91% of high-income countries have surveillance systems in place.

In Africa, a study by Zaganjor et al. (2016), indicated that up to 300 000 NTD babies are born per year globally; while up to 88 000 NTDs babies die per year. Again, 29% of neonatal deaths in low-income countries are related to NTDs. Lo, Polšek, & Sidhu, (2014) affirmed that there is a high incidence of NTDs in low-income countries compared to high-income countries. Sorri & Mesfin, (2015) reported a high incidence of NTDs in Ethiopia, 61/10000, births, the majority being spina bifida and that 92% of NTDs babies are born to married mothers. Sadik, Babikir, & Arbab, (2017) in Sudan identified a high incidence of neural tube defects with up to 73% being spina bifida. Mothers were young, often in stable relationships.

Similarly, Airede (1992) presented the picture of the incidence of NTDs in Middle Belt Nigeria with incidence of 70/10000, (the majority being spina bifida, whereas in Tanzania, a high incidence of NTDs was at 26/10000, (Salih et al., 2014).

With regard to Northeast Nigeria, (Bello et al., 2008) presented a high incidence of neural tube defects of 43/10000 births, mostly of spina bifida. Equally, Anyanwu, Danborno, & Hamman, (2015) reported high incidence of neural tube defects of 27/10000 in Northwestern Nigeria (Kano). Mothers were counted on admission in this prospective study. Presenting a different picture, North Central Nigeria had an incidence of NTDs of 5/10000 births and many of the babies were born out of consanguineous marriages (Uba et al., 2004).

In some SADC Countries, such as South Africa, the incidence of neural tube defects in Cape Town, ranged from 17.4 to 6.3/10000 births over 20 years, Buccimazza et al. (1994), in other words, 6/10000 of NTD, which reflects a very low incidence of neural tube defects in comparison to Northeast and Northwest Nigeria. However, this picture cannot be generalised to the whole country. In the Eastern Cape part of South Africa, Marasas et al. (2004) reported a high incidence of neural tube defects of 61/10000 births in rural Transkei. It was stated that consumption of mycotoxins in contaminated maize could be the reason for fumonisins, which was proposed, could predispose babies to NTDs. A similar study in rural Limpopo Province, high incidence of 35/10000 births was found and mycotoxin (fumonisins)-contaminated maize could be the cause. Table 2 below depicts very high incidence of NTDs in some African countries, some being 61-70/10000, far above 8/10000, which justifies a need for an intervention.

Table 2: Summarized NTD incidence in some African Countries.

Region	Country	NTD incidence per 10000 births	Year
North	Ethiopia	61/10000	2015
West	Nigeria – Middle Belt	70/10000	1992
	Nigeria – NorthEast	43/10000	2008
	Nigeria – NorthWest	27/10000	2015
	Nigeria-NorthCentral	5/10000	2004
East	Tanzania	26/10000	2014
Southern	South Africa – Eastern Cape (Transkei)	61/10000	2004
	South Africa– Limpopo	35/10000	2004
	South Africa – Western Cape (Cape Town)	6-17/10000	1994

In other SADC countries, such as Angola, Zambia, Zimbabwe and Botswana, incidences of NTDs appeared not to be well documented. In Botswana, (Zash, Makhema, & Shapiro, 2018) conducted various studies on the possible association between the use of an antiretroviral drug (dolutegravir) by mothers and the incidence of neural tube defects babies. However, there was no evidence of an association between the two at that time.

In Malawi, (Msamati, Igbigbi, & Chisi, 2000) found that the incidence of neural tube defects was 6.5/10000. Interestingly, surveillance data on the incidence of neural tube defects in other African countries such as Tanzania, Kenya and Mozambique were limited, as generally reflected in global reports.

In Namibia, no study was found on the incidence of neural tube defects. However, a few sources reflected on the high incidence of birth defects in general. In 2006, Tjaronda cited the Global Report Identifies Birth Defects Problem - New Era Live, which indicated that 53/1 000 babies born in Namibia had birth defects. In SADC countries, Namibia is ranked number 11 among SADC countries with the highest number of children born with birth defects. Furthermore, Country Profile - Namibia, on Food Fortification Initiative (FFI) reported that the incidence of neural tube defects in Namibia is estimated at 15/10000 births.

2.2.2. The burden

According to Blencowe et al. (2010), the estimated incidence of NTDs in the world is about 300 000 new cases per year, resulting in 41 000 deaths and 2.3 million disability adjusted life years. Blencowe et al. (2010) further stated that NTDs constitute the third largest burden of congenital anomaly (after congenital heart disease and Down syndrome). A study by Zaganjor et al. (2016) reported on the global burden of NTDs as follows; up to 300 000 NTDs affected babies born globally per year. In addition, approximately 88 000 babies affected by neural tube defects die each year. In low income countries, up to 29% of neonatal deaths were attributed to NTDs.

Lo, Polšek & Sidhu, (2014) affirm that the burden of NTDs are at least twice as high in low income than high income countries with a median of 16/10000 live births, although, the maximum burden goes up to 124/10000 live births in low income countries. Correspondingly, Berihu et al. (2019) reported a high burden of NTDs in Tigray (Ethiopia) with up to 77% who were stillborn. This means that the high burden was not only reflecting high incidence, but also the high cost implications related to transportation, hospitalisations, surgery and care as well as costs related to caregivers. It can be concluded that other social and emotional burdens that may not be quantifiable were prevalent. Additionally, Lo, Polšek, & Sidhu, (2014) reported limited data on NTDs in low and middle-income countries during the period of 2000 to 2013. Approximately, 190 000 neonates were born with NTDs each year during the same period in low and middle-income countries. This means that only two countries from Africa, namely, Cameroon and South Africa contributed studies to 37 countries that had satisfactory data for review.

2.2.3. Risk factors

These risk factors are classified as being either genetic or environmental, though with complex interactions between them (Padmanabhan 2006). Over the years, more progress has been made in the understanding of environmental than genetic factors. Historically, Bjorklund & Gordon (2006) report that the association between NTDs and diet was noticed during the Dutch famine in 1944. Later, in 1965, Hubbard and Smithells documented the link between NTDs and folic acid Salih et al. (2014). Imbard et al. (2013) state that NTDs sensitive to folate fortification ranged from 10 to 80% in different environments.

In a systematic review, Salih et al. (2014) presented risk factors as follows:

- Maternal Diabetes
- Maternal obesity (BMI \geq 30kg/m²)
- Anticonvulsants e.g. valproic acid and carbamazepine
- Exposure to lead, arsenic and tetrachloroethylene
- Sulphonamide
- Trimethoprim
- Hyperthermia e.g. following maternal flu or use of a sauna
- Maternal exposure to pesticides at home
- Consumption of maize or corn contaminated with fumonisins (mycotoxins)
- Maternal and paternal occupations in agriculture, cleaning, welding, transport, health care and painting
- Living near coal mines
- Women of lower socioeconomic status
- Consanguinity

According to Padmanabhan (2006), genes play an important role in the formation of NTDs, likely by interacting with environmental factors such as folic acid, Vit B12 and homocysteine. In addition, future research needs to focus on gene interaction with other genes, nutrients and other elements.

2.2.4. Diagnosis

Historically, NTDs were only diagnosed after birth when they were clinically visible. Prenatal diagnosis was introduced following the discovery of the use of amniotic fluid to determine alpha feto protein and acetyl cholinesterase levels between the 14th and 23rd week of gestation (Smith et al., 1979).

In most cases, high levels of amniotic alpha fetoprotein and acetyl cholinesterase correlate with the presence of NTD affected babies. Secondly, Wilson et al. (2014) reported that ultrasound has become the mainstay of prenatal diagnoses of NTDs, overtaking alpha fetoprotein and acetyl cholinesterase tests. Prenatal diagnoses of NTDs were later utilised as a basis for counselling and termination of pregnancy in countries where it was legalized (Salih et al., 2014). In countries with limited resources, most NTDs are only diagnosed after birth. These defects are clinically visible as large encephaloceles and myelomeningocele, for example.

However, occult NTDs can still be missed, since they may require the use of imaging investigations such as computerized tomography scanning and magnetic resonance. Furthermore, Salih et al. (2014) list other causes of raised alpha fetoprotein, namely conjoined twins, Turner syndrome, omphalocele, gastroschisis, extrophy of cloaca.

2.2.5. Prognosis

The effects of neural tube defects could result in different outcomes. According to Mobasher, (2007) and Lo, Polšek, & Sidhu, (2014), NTDs led to spontaneous abortions, early neonatal deaths or long-term disabilities. Similarly, Crider et al. (2014) state that NTDs were associated with high mortality, morbidity, disability, as well as psychological and emotional stress. Examples of morbidity caused by spina bifida were lower limb paralysis and dysfunction of urinary bladder and bowel. Blencowe, Cousens, Modell, & Lawn, (2010) stated that in Sub-Saharan Africa, an estimated 17,500 neonatal deaths were due to NTDs compared to 8, 500 neonatal deaths in North Africa and the Middle East. Table 4 presents various categories of NTDs, their features and sequelae in order to have a general understanding of the concept of NTDs, including prognosis.

Table 3: Categories of neural tube defects, their features and sequelae

	Anencephaly	Encephalocele	Spina bifida cystica
Cause	Failure Of closure of the anterior (cranial) neural arch.	Failure of closure of the anterior (cranial) neural arch at a later stage of embryogenesis than anencephaly.	Failure of closure of the posterior (caudal) vertebral arch. Most commonly affecting the lumbo-sacral region and usually associated with hydrocephalus (blockage of drainage of the cerebrospinal fluid).
Clinical Features	Absence of variable amounts of brain, spinal cord, nerve roots and meninges.	Sack containing brain tissue herniates through midline skull defect, usually occipital	Herniation of the meninges through a defect in the lower spine (meningocele) or severe forms include also herniation of dysplastic spinal cord (myelomeningocele). Hydrocephalus resulting in extra fluid around the brain and raised intracranial pressure.
Prognosis & Sequelae	Stillbirth or neonatal death.	Variable-high mortality from meningitis. With surgical repair, long-term outcome varies from normal function to severe multi-domain impairment.	Variable levels of disability including: <ul style="list-style-type: none"> - <i>Neurological</i>: sensory motor defects, learning disabilities, epilepsy. - <i>Orthopedic</i>: contractures, joint dislocation, talipes. - <i>Functional</i>: bladder and bowel dysfunction.

Source: Blencowe et al. (2010)

Although babies with NTDs could live with disabilities, there was also a high probability of death. Salih et al. (2014) affirmed that 75% of babies with encephaloceles die before their first birthday. However, Thompson (2009) pointed out that multidisciplinary management greatly improved outcomes of neural tube defects. Mildly affected babies may survive to adulthood without disability. Furthermore, a study by Blencowe et al. (2010) on congenital abnormality deaths and number of neonatal deaths due to NTDs for 2005 by the WHO region, the table 4 focused on NTD-related deaths in Sub-Saharan Africa.

Table 4: Estimated congenital abnormality deaths and numbers of neonatal deaths due to NTDs for 2005 by the WHO region (low-income/high neonatal mortality countries) - Sub-Saharan Africa

Region	Estimated NTDs incidence per year	Estimated total neonatal deaths due to (uncertainty p/year NTDs range)	Estimated number of neonatal deaths due to NTDs p/year	% of neonatal deaths due to NTDs p/year
West	34 500	(18,000–69,000)	8000	23
South	3000	(2,000 – 6,000)	1000	33
East	30 000	(18,000 - 49,000)	6500	22
Central	12 000	(3,000 – 27,000)	2000	17
Total	79 500	(55,000 - 122,000)	17 500	22

Source: Blencowe & Cousens, (2010).

Table 4 was derived from an article by Blencowe et al. (2010) obtained from systematic searches in 193 countries of the WHO regions for prevalence and case-fatality rate data with a focus on Sub-Saharan Africa. Southern Africa (in which Namibia is located) emerged to have a lower incidence of NTDs (3000 per year) in

comparison to other regions. However, although there was lower incidence of NTDs, the numbers of neonatal deaths were 1000 per year, which is 33%. The wide range of reported deaths reflected different data drawn from various studies. This depicted that there is either an inadequate response from the region or lack of documentation to get a clear picture, which justified a need for further investigation.

2.2.6. Operative Treatment

The treatment of NTDs is mainly surgical. Post-natal repair of NTDs has been the standard treatment long before in-utero foetal surgery was introduced. Post-natal surgery involves cosmetic repair of the defects, sometimes with additional procedures to improve the quality of life or to deal with complications. Surgeons are often faced with challenging ethical considerations such as whether or not to give operative treatment. Outcomes can be satisfactory for mild cases, but can be disappointing with severe cases. Very often, neurological deficits cannot be improved. Most procedures remain only palliative at best.

In 1997, Tulipan & Bruner, (1998) introduced in utero foetal repair of myelomeningocele with a good outcome, for example: reduction in mental retardation and the need to do ventriculoperitoneal shunting within one year. Morbidities of the in-utero foetal repair include pre-term labour and uterus dehiscence at birth. It is also stated that spinal defects often lead to urinary and faecal incontinence as well as paraplegia.

Salih et al. (2014) stated that in-utero foetal surgery reduced toxic damage of neural tissue by amniotic fluid and reduced brain herniation through foramen magnum as well as hydrocephalus in babies with spinal defects.

Similarly, Wallingford, Niswander, Shaw, & Finnell (2013) asserted that *in-utero repair* of spinal NTDs was associated with better clinical outcomes than post-natal repair. Even after surgical repair, many clinical problems persisted, leading to emotional challenges, financial and societal costs. In the USA, Salih et al., (2014) reported that annual surgical and medical costs for neural tube defects amounted to more than U\$ 200 million, while direct and indirect costs per person were more than U\$ 250 000.

In addition, in countries where abortion was legalized, counselling and early termination of pregnancy was offered to women found to have babies affected by NTDs, following accurate prenatal diagnosis. This practice is not universally followed because of differing ethical, cultural and religious considerations (Salih et al., 2014).

2.2.7. Prevention

Following the initial reports by Imbard and Smithells in 1965, that folic acid intake can reduce NTDs, several studies (Copp et al., 2013), subsequently provided strong evidence in support of their findings, namely:

- The MRC Vitamin Study (randomized double blind trial) in 1991 reporting prevention of recurrent NTDs (MRC Vitamin Study Research Group, 1991).
- The randomized clinical multivitamin trial in Hungary in 1992, reporting prevention of first occurrence NTDs (Czeizel & Dudas, 1992).
- The clinical trial in China in 1999 reporting reduction in NTD prevalence following folic acid supplementation (Berry et al., 1999).

- The introduction of mandatory fortification of bread flour in USA in 1998, following a report by Oakley, Erickson, & Adams (1995) to urgently increase folic acid consumption.
- By October 2017, 81 countries worldwide carried out mandatory food fortification (Wald et al., 2018).
- Promoting consumption of green vegetables (Zhang et al., 2008).
- Folic acid supplementation or fortification can reduce first occurrence of NTDs by up to 70% Mustafa (2014) and recurrent NTDs by up to 70% (Blencowe et al., 2010). NTDs are the most common disabling birth defects and can be reduced by up to 80% if women of childbearing age consume 400µg of folic acid daily periconceptionally (Salih, Murshid, & Seidahmed, 2014).

According Crider et al. (2014), maternal red blood cell folate of more than 906 nmol/L in the periconceptional period was associated with a low risk of development of NTDs. This meant that for the mother who conceived with a folate concentration of less than 906 nmol/L, there was a high chance for the baby to have a NTDs. Ideally, all mothers should have this information in order to take specific preventive measures. Nevertheless, a number of studies agreed that in low-income countries, information on specific preventive measures was not readily available. Salih et al. (2014) proposed different preventive measures for neural tube defects (folate and non-folate sensitive) namely; folate rich diet, folate supplementation and folate food fortification. The consumption of folate rich food, such as fresh and frozen leafy vegetables, liver, wheat bread, citrus, fruits juices and beans has the potential to increase the maternal red blood cell folate to levels above 906 nmol/L.

Periconceptional folate supplementation prevents both first occurrence as well as recurrence of neural tube defects. Food folate fortification can reduce neural tube incidence by up to 50%.

However, not all countries have introduced mandatory food fortification policies for wheat, maize, rice and millet. In terms of non-folate sensitive measures, Salih et al. (2014) further identified avoidance of obesity, smoking and consanguineous relationships as preventive measures. Folate food fortification reduced neonatal mortality due to neural tube defects in Argentina (Blencowe et al., 2010). It is clear that if countries have not implemented some of the cited preventive measures, there is likelihood that the prevalence of NTDs will be high.

Other risk factors require factor specific interventions such as:

- Providing vitamin B12 in addition to folic acid.
- Avoiding the use of folic acid inhibitor anticonvulsants in women of reproductive age.
- Offering genetic counseling in selected cases.

2.3. KEY FINDINGS AND CRITICAL REFLECTIONS

Scholarly contributions by Crider et al. (2014), Salih et al. (2014) and Blencowe et al. (2010) are noted. NTDs comprise a wide range of primarily ectodermal developmental defects associated with variables malformation of tissues derived from mesoderm (Salih et al., 2014). These defects may result in abortions, stillbirths, deaths or survival with lifelong disabilities. The incidence of NTDs varies widely from country to country worldwide and from region to region within the same country.

There are many risk factors, which can be classified as folate sensitive and non-folate sensitive. Furthermore, folic deficiency is a key risk factor. The inverse relationship between the maternal red blood cell folate concentration and the incidence of NTDs is evident. The cut off level of 906 nmol/L below which folate sensitive NTDs incidence is expected to be high was observed. The use of red blood cell folate values was recommended (Cordero et al, 2015) in the strategies to prevent NTDs, because it reflects a longer duration of the result.

The serum folate estimates the levels over a short duration, which may not represent a correct folate status in the population. While there is no curative treatment for NTDs, surgical and multidisciplinary interventions provide some improvement in the quality of life of those affected. Finally, prevention strategies are key to the reduction of burdens presented by NTDs.

The following key points should also be noted:

- Folic acid supplementation / fortification reduces the occurrence of NTDs if given periconceptionally (Mustafa, 2014).
- Folic acid fortification can reduce NTDs related infant mortality by 38.8% and perinatal deaths by 65% (Sayed et al., 2008).
- The optimal population red blood cell folate cut off level for most folate sensitive NTDs is about 906 nmol/l at 28 days gestation (Crider et al., 2014).
- Many countries have already adopted periconceptional folate supplementation or mandatory food fortification to prevent of folate sensitive NTDs (Mustafa. 2014).
- Red blood cell folate should be used in research rather than serum folate (Cordero et al., 2015).

- NTDs incidence of 8/10000 births or more may be regarded as high, thus requiring corrective interventions (Crider et al., 2014).

Some of the important advances on the topic of NTDs include introduction of mandatory folate food fortification and in-utero surgical repair, better understanding of genetic predisposition regulating methylation and planar cell polarity, primary and secondary neurulation disorders as well as post closure disorders (Copp, 2013). The following gaps in the literature were identified. There is a lack of adequate data on NTDs, especially from low-income countries. Detailed studies on mechanisms on how NTDs develop are still ongoing, especially from the genomic perspective. There is an incomplete understanding of similarities or differences between countries where NTDs incidences are high. Inadequate emphasis was put on community education and gardening for vegetables and fruits. In addition, future research should focus on folate resistant NTDs, genome wide gene sequencing, related epigenetic phenomena and stem cell studies. In Namibia specifically, no study on NTDs was found, hence the need for a groundbreaking baseline study on the subject.

2.4. SUMMARY

The chapter explained the congenital malformation described as NTDs. This include the types and mechanisms of development. This chapter also covered essential topics on NTDs from incidence to prognosis. Gaps in literature were pointed out. The high incidence in developing countries remains a great concern. Folic acid deficiencies remain the most important preventable risk factors, based on the documented inverse relationship between the level of maternal periconceptional red blood cell folate and incidence of NTDs. There is limited documentation of information on NTDs in developing countries and hence the justification of this study. It became clear that NTDs cause a heavy burden in developing countries. While diagnosis is relatively easy in most cases, treatment is only palliative. Prevention of folate sensitive NTDs has proven success worldwide, but is not without challenges. Many scholarly publications were reviewed, mostly systematic reviews that will be valuable in guiding the next chapter on methodology. Only English literature could be reviewed.

CHAPTER THREE: RESEARCH METHODOLOGY

3.1. INTRODUCTION

The preceding chapter reviewed the literature and studies that are relevant to this study. This chapter discusses research methodology, design and instruments used in collecting data on the incidence of NTD babies in two public hospitals: Onandjokwe and Oshakati of Oshikoto and Oshana regions respectively. In addition, the populations, sampling technique, research instruments, procedures used to gather data and analysis, are also presented. The study context is given in details in chapter two.

3.2. RESEARCH DESIGN AND METHOD

According to Joubert, Ehrlich, Katzenellenbogen, & Karim, (2007), research design refers to the structural approach followed by the researchers to answer a particular research question. It is also referred to as the ‘architecture’ of the study, because the choice of the research design determines how one samples the population, collects data, analyses the data, costs and ethical considerations. Creswell (2014) categorises research design into three forms of inquiry, namely: qualitative, quantitative and mixed-method approaches that provide specific guides for actions in a research study.

A quantitative design is a formal, objective, systematic process for obtaining quantifiable data about the variables of a study. A quantitative approach was therefore used to assess the incidence, and identify risk factors for, NTDs babies in the two hospitals. This study employed a quantitative approach to address the established research questions.

In the quantitative approach, Mouton (2001) describes two different types of research; exploratory and descriptive. In this study, a descriptive approach was selected and a survey was administered as a method to determine the incidence of neural tube defects from the maternity ward records. Secondly, within a descriptive approach, a survey questionnaire was developed and administered to participants face to face to establish and document risk factors of NTDs. A cross-sectional design was selected due to the fact that this study was conducted in the present time in a single occasion within a fixed period to examine what currently exists (Hulley, Cummings, Browner, Grady, & Newman, 2007). In addition, Rivers, & Wilson (2016) outline the advantages of a cross-sectional study as follows:

- Used to prove and/or disprove assumptions;
- Not costly to perform and does not require time;
- Captures a specific point in time;
- Contains multiple variables at the time of the data snapshot;
- The data can be used for various types of research;
- Many findings and outcomes can be analysed to create new theories/studies or in-depth research.

The most applicable advantages to this study are that it is not costly to perform, less time consuming and captures a specific point in time. Moreover, it also identifies subjects for new research studies. In this study, two designs were used, a hospital-based case-control and prospective cross-sectional. The study prospectively registered all birth outcomes (neural tube defects or normal) at two hospitals with large numbers of births in Oshakati and Onandjokwe Intermediate Hospitals. The aim was to determine the incidence of

neural tube defects in this population (women who deliver at these hospitals) over 12 months. Additionally, a case-control design was used in these hospitals to obtain baseline data for the risk factors associated with neural tube defects. These study designs were found suitable to determine incidence and risk factors of NTDs among mothers who delivered babies with NTDs (cases) and compare them with those who delivered babies without NTDs (controls) between 1 September 2016 and 31 August 2017. NTDs are grouped among rare health conditions; therefore, case-control study is appropriate for their evaluation as used in this study.

3.2.1. Variables

Brink et al, (2012) define variable as a quantifiable element that changes or varies, which the researcher has to manage and assess. Some variables were manipulated while others were controlled. Besides, although there are different types of variables, Brink et al., (2012) clarified two types of variables, namely: dependent and independent variables. Dependent variables reflect the outcome, while independent variables precede the outcome. In this study, the incidence of NTDs was identified as a dependent variable, whereas the risk factors of neural tube defects were identified as independent variables. Thus, this study explored the correlation/association between two types of variables as defined NTDs above. Brink et al. (2012) define correlation as the extent to which values of one variable (x) are related to the values of a second variable (y). This means, correlation can be either positive or negative. The findings of this study suggested a positive correlation between high incidence of neural tube defects and some risk factors, such as environmental and socio-economic influences. The correlations are confirmed by

the p-value of less than the 'conventional frequentist threshold' (p-0.05) (Gagne, Thompson, O'Keefe, & Kesselheim, 2014).

However, despite the fact that this study utilised the conventional threshold of 0.05, a study by Gallin et al. (2003) proposed that the threshold of 0.05 be increased to 0.10 depending on the availability of research cases (Gallin et al., 2003). Mean maternal red blood cell folate levels were measured in both cases and controls. The possible variables and risk factors associated with NTDs were considered. Salih, Murshid, & Seidahmed (2014) categorised some of the risk factors as follows: low red blood cell folate, chromosomal and other genetic factors, maternal obesity (derived from weight and height), hyperthermia, maternal cigarette smoking, alcohol, and consanguinity.

In addition, socio-economic status - employment, drug use (Valproic acid, Carbamazepine, Sulfonamides, methotrexate), age, diet, diabetes, region, educational level, rural and urban were listed. Other factors identified were: gravidity, ante-natal care (ANC) attendance, ANC folate supplements, gestation, parity, body mass index (BMI) [height /weight], and hemoglobin and family history. The detailed discussions of the findings in relation to variables are offered in Chapter 5. Quantitative approach findings are presented in a numerical form and quantified, which allows for the use of statistics to analyse the collected data drawn from the research population and sample.

3.3. POPULATION

The research population in research entails a complete set of people or objects with specified and common characteristics that are of interest to the research (Hulley et

al., 2007; Brink et al., 2012). The specified and defining characteristics can also be clinical, demographic or temporal.

The defining characteristics can be categorised as follows:

- Clinical and demographic characteristics – define the target population as a large set of people worldwide to whom the results may be generalised.
- Geographical and temporal characteristics – define a subset of the accessible population that is available for the study.
- The intended study sample is the subset of the accessible population that the researcher seeks to include in the study.
- The study sample is a group of subjects that participates in the study. To apply the above characteristics, the researcher developed selection criteria for inclusion or exclusion in the sample of the population studied.

3.3.1. Inclusion Criteria

This set of criteria defines the main characteristics of the target population that is appropriate to the study, namely: demographic, clinical, geographic and temporal (Hulley et al., 2007). In these criteria, specific populations relevant to the research question and efficiency for the study were listed in table 5 below.

Table 5: Selection criteria for inclusion for the assessment of incidence of NTDs

Characteristics	Example of Cases	Example of Controls
Demographic	All mothers delivering babies	All mothers delivering babies
Clinical	Mothers with NTD babies	Mothers without NTD babies

Geographic	Mothers at Onandjokwe and Oshakati Hospitals	Mothers at Onandjokwe and Oshakati Hospital
Temporal	From 01 September 2016 To 31 August 2017	From 01 September 2016 To 31 August 2017

The following were the selection criteria for inclusion (both cases and controls) the researcher employed to determine respondents of the study. All women giving birth in Oshakati and Onandjokwe hospitals from 1 September 2016 to 31 August 2017 were recorded and total births were calculated. For each identified case of NTD, a control was selected to compare characteristic and risk factors.

In addition, all women giving birth to babies with or without NTDs were recorded and all NTD babies identified underwent clinical physical examination with or without foetal brain ultra sound scan. Blood samples for red blood cell folate were drawn from consenting cases and controls. In this study, respondents were able to speak Oshiwambo or English. The intended population was all mothers who delivered in Onandjokwe and Oshakati Hospitals between the set dates, within the same month and week. The researcher was interested in assessing the incidence and identifying the related risk factors. The actual population was 15 mothers whose babies had NTDs. To develop Inclusion Criteria for Controls, the initial controls selection criteria were; mothers of the same age, haemoglobin (Hb), parity, delivering at the same time, with the same weight and height as well as same region.

However, it was practically impossible to satisfy all these criteria because birth happens spontaneously and randomly, which could not be controlled. As a result, the researcher employed the following selection criteria for controls: mothers who delivered in the same hospital, delivered within the same week and month, and delivered a baby without NTDs (normal babies). No mother was excluded on the basis of language or age.

3.3.2. Exclusion Criteria

These criteria specify the subsets and characteristics of the population that were not included in the study, as listed in Table 6 below.

Table 6: Selection criteria for exclusion for the assessment of incidence of NTDs

Exclusion Criteria	Characteristics	Example Cases	Example Controls
	Interferes with the success of follow-up efforts	Mothers with NTD babies referred to Oshakati or Onandjokwe hospitals for management	Mothers without NTD babies referred to Oshakati or Onandjokwe hospitals for management
	Inability to provide good data	Incomplete documentation of the case	Incomplete documentation of the control
	Being at high risk of possible adverse effects	Babies born by vulnerable persons	Babies born by vulnerable persons

Table 6 presented the exclusion criteria that assisted the researcher to select suitable respondents for the study. The researcher observed a few cases of mothers with NTD babies referred to Oshakati and Onandjokwe hospitals for management during the study. However, such babies were not counted and recorded, since they were not part of the study. Mothers who could not give consent to enter the study and those babies born by vulnerable persons were not encountered. Likewise, no babies born by mothers taking drugs that interfered with red blood cell folate determination such as methotrexate and aminopterin were encountered.

3.4. SAMPLING

The word sampling refers to the subset of the population of the participants (people) who meet the entry or inclusion criteria (Hulley et al., 2007: 27). It is further stated that non-probability sampling is found to be suitable for clinical research, which is made up of people who meet the inclusion criteria and are easily accessible to the researcher. There are different types of non-probability sampling, namely:

convenience sampling, consecutive sampling, quota sampling, purposive sampling and snowball sampling (Brink et al., 2012). In this study, non-probability consecutive sampling was applied to each group (cases and controls) (Brink et al., 2012). This approach was appropriate in this study because the researcher was interested in studying “rare or unpredictable phenomena”, in this case, NTDs. Hulley et al. (2007: 140) referred to the convenience sampling method (consecutive sampling) as ‘availability sampling’, as it involves the choice of readily available participants.

3.4.1 Sampling procedure

Each baby delivered in the hospital is routinely examined by a doctor for identification of NTDs and recorded in the hospital register. The mother of the baby is then identified by the researcher or research assistant as a participant in the study if she agrees after all relevant information were given to her. She then becomes part of the cases. A corresponding mother with a normal baby delivered within the same week is then identified as a control. This process was continued over a period of 12 months until all NTD babies, their mothers (cases) and the control mothers were identified and listed if they met the inclusion criteria. The accuracy of the diagnosis of NTDs was sometimes confirmed with ultrasound or CT scan of the brain. This method (consecutive sampling) was used to ensure that every NTD baby was included in the study, in line with the inclusion criteria. Consecutive sampling was used in this study because relevant samples were not obtainable by other means. It has the advantage of minimizing volunteerism and other selection biases by consecutively selecting subjects who meet the entry criteria. This approach was preferred because it could be applied to the study, which might take a long period,

covering seasonal variations and other temporal changes, which were part of this study. This sampling method guaranteed that all eligible participants were given equal chance to be included in the study, minimizing bias. The researcher ensured that all mothers who delivered in the two hospitals - with a specific focus on those who gave birth to NTDs babies and those whose babies were not affected - were selected.

The researcher recognized the limitations of this type of sampling, namely that it does not contribute to generalization and that bias may be present (Brink et al., 2012). However, due to the nature of the study, which was of rare and unpredictable phenomena, the researcher was satisfied that it was suitable.

3.4.2. Sample size

Sample size of the study calculated separately for both the incidence and risk factors to neural tube defects. The study prospectively enrolled all births in both hospitals, recorded the cases with neural tube defects and calculated the incidence in those hospitals over one year. There was no an estimation of the population incidence, as this would have required sample sizes that would only be possible to achieve with the introduction of a national birth registry for the collection of neural tube defects.

Thus, considering the incidence of neural tube defects to be 5 -10 per 10,000 births (Sayed, et. al, 2008) and using a single proportion formula at 95% CI and 0.5% margin of error, a total of approximately 100,000 pregnant mothers would need to be enrolled if the lower estimate were to be detected in the hospitals (5 per 10,000 births). For assessing risk factors for neural tube defects, and considering 95% confidence level (CI), 80% power, control to case ratio of 1, minimum odd ratio of 2, and 10%

nonresponse gives a minimum sample of 222 cases of NTDS and 222 controls. Although, this was the scientifically calculated sample size, due to rarity of the condition, such a study would take 15 – 22 years to complete, which would be too long. Gagne et. al (2014) stated that waiting for the large number of rare conditions to be reached per year creates barriers for research to be conducted, the advancement of knowledge, and treatment to be provided to the affected people.

In line with the abovementioned argument, the study adopted the Bayesian model, which takes into account the pre-existing knowledge, to address challenges related to small populations in the field of research on rare conditions (IRDIRC, 2016). There were 17 NTD babies identified in the two hospitals over 12 months, however two were excluded because the diagnosis of NTD could not be verified due to incomplete clinical information. The remaining 15 babies were available for the identification of 15 cases (mothers) and 15 controls. The study sample size was categorised into sections: cases were mothers of babies with NTDs and controls were mothers of babies without NTDs as indicated in Table 7.

Table 7: Sample Selected from the Population.

Hospitals	Cases	Controls	Total
Onandjokwe	9	9	18
Oshakati	6	6	12
Total	15	15	30

In table 7 above, the sample size consists of mothers of babies with NTDs (cases) and mothers of babies without neural tube defects (controls). The researcher used

consecutive sampling to identify the available cases at each hospital, which were nine and six respectively. A corresponding number of controls were selected from the population of mothers who delivered during the specified period. The sample size was quantitatively small, but was used complemented by the Bayesian model, which takes into consideration the pre-existing and accumulated knowledge (International Rare Disease Research Consortium (IRDIRC), 2016).

3.5. DATA COLLECTION INSTRUMENTS AND PROCEDURE

The researcher employed different instruments, namely: questionnaires, maternity records and blood samples. A structured questionnaire, written in English and Oshiwambo to cover those who could not speak English, was used to collect data. The questionnaire was used to collect quantitative data for the incidence of NTD babies at maternity wards at the two hospitals. Most of the questions were closed ended with a Likert rating of yes or no answers, while others were open in nature with a space for a short answer. Hospital records were reviewed to obtain data such as height, weight and haemoglobin. After the completion of the questionnaire, the researcher conducted a pilot study. Joubert et al. (2007) define a pilot study as a mini-study, which tests parts of the study before the main study. The purposes were to check the methods (instruments and logistics), obtain data to assist in sample size estimation and test adequacy of field training.

The instruments utilised in this study were pilot tested in August 2016 in the two hospitals, Onandjokwe and Oshakati in Oshikoto and Oshana regions. Pilot studying enabled the researcher to identify the appropriateness of the instrument and challenges associated with the procedures of collecting data. Primarily, the researcher

or research assistant clinically verified the type of NTDs recorded in the hospital register. However, since some of the NTDs were not clinically recognisable, confirmation of hydranencephaly was done with an ultrasound or CT scan imaging. The instruction guide that was developed included the use of ultrasound or CT scan imaging to confirm the diagnosis of NTDs before the questionnaire was administered to participants. This method supplemented data collection tools to strengthen the quality of data and served as a form of triangulation to improve the credibility of the results.

3.5.1. Questionnaire

The researcher translated the questionnaire from English to Oshiwambo. According to Hulley et al. (2007: 232), questionnaires have the following advantages, which informed the researcher's decision to select it as a research instrument:

- Are more efficient than interviews and have a uniform way to administer;
- They are less expensive and require less time;
- They are easily standardised;
- They provide the possibility of anonymity because the subjects' names were not required on the completed questionnaires;
- There is less opportunity for bias, as they are presented consistently.

All the above-mentioned advantages are applicable to the context of this study. One potential disadvantage to the participant is that they are not given unlimited freedom to speak freely. However, there is a greater advantage to guide the participants when discussing unfamiliar subjects on NTDs.

3.5.2. Questionnaire development

The questions included in the questionnaire were based on the risk factors identified in the literature review. The aim was then to compare similarities or differences with what is already known and applicable to local population. The outcome could guide future focused research. The questionnaire guide consisted of four sections and the instructions on how to answer the questions. Section A: demographic data, Section B: Socio-economic status, Section C: Health indices and Section D: Knowledge of NTDs. Section A presented demographic information; hospital number, date of birth, age and regions. Section B focused on socio-economic status of participants, such as employment, education and marital, while Section C consisted of Health indices such as weight and height, body mass index, haemoglobin, pregnancies, deliveries, HIV and other diseases. Section D focused on knowledge on NTD, family history and types of NTDs. Likert scale was used for different questions; with Yes or No and often or rarely to provide answers in line with local cultural norms.

3.5.3. Piloting questionnaire

At the pilot stage, since there was no instruction to offer pre-counselling prior to the interview, one participant (mother with NTDs baby) started crying when questions were posed to her. The researcher also noted that the participant started asking questions whether NTDs can be cured and the causes. As a result, the researcher developed the instructions guide, stipulating the importance of pre counselling. The questionnaire instruction guidelines were developed and distributed to assistant researchers (see Annexure J). The pilot study helped the researcher to become aware of the need for the instruction guide and pre-counselling of participants. The pilot study involved an explanation to participants about what research is, the need for it,

the rights of participants and the questions to be covered. The researcher then had to assess the understanding and emotional response of the participants to the process, before asking them to voluntarily sign consent forms. One case (only 1 case found) and one control took part. The questionnaire was then finalised after adjustments were made to it based on lessons learned from the pilot study.

3.5.4. Pilot study outcomes

The following outcomes of the pilot study were realised:

- The applicability of the instrument was confirmed
- The emotional impact of the study on the participants was appreciated. This happened when the participants started crying when she realised the NTDs affecting her baby (spinal bifida) cannot be cured.
- The emotional impact prompted the researcher to design an instruction guide for the researcher and assistant researcher to ensure empathy during the interview and to offer appropriate pre and post counselling.

An ultrasound scan was used in the process of examination and verification of types of NTDs was added. A few changes were made to the instruments after the pilot study, mostly re-categorisation of questions, developing instruction guides and addition of some questions that helped to clarify other questions.

3.5.5. Administration of the questionnaire

The researcher personally administered the questionnaires to the participants face-to-face. However, since the study was conducted over 12 months and the researcher was not present throughout the whole period of the data collection, two senior doctors were identified in the wards of each hospital to serve as assistant researchers.

The assistant researchers were briefed on the content of the questionnaire and trained on the procedure of administration by the researcher over a period of one day per each hospital.

A few questions that were not very clear were clarified to the mothers. Since the questionnaire was in both English and Oshiwambo, participants found it easier to understand them. The researchers identified the mothers of babies with and without NTDs (normal babies) based on clinical criteria and administered the same questionnaire. All mothers with and without NTD babies were counselled and asked to give informed consent for blood samples to be taken for red blood cell folate content analysis. The control group comprised the mothers who gave birth to babies without NTDs. The questionnaire took 40-60 minutes to complete because the researcher needed sufficient time to explain the objectives of the study to participants.

3.5.6. Blood Samples

After the explanation and counselling, each participant was asked to give informed consent for blood samples to be taken for red blood cell folate content analysis. Blood samples were also collected at post-natal clinics within one week from the determination of the cases and controls for red cell folate, which correlates better with tissue folate levels than the serum folate. Health personnel followed a standard sterile procedure to draw a blood sample of 3 to 5 ml of venous blood from each participant. The blood sample was put in the sealed ethylenediametetraacetic acid (EDTA) tube, coded and transported at 2 to 8 degrees Celsius with temperature monitoring to Namibia Institute of Pathology (NIP) laboratory. After entering the

sample in the laboratory information system (Meditech), the sample was then sent to Lancet Laboratories in South Africa for red blood cell folate analysis using Abbot Architect Analyzer. Universal precautions were followed to handle the sample. All standard laboratory protocols were followed for storage, transportation, analysis and calculation of red blood cell folate, until the results were available on-line using a password.

3.5.7. Maternity records review

Haemoglobin (Hb) values of participants were taken from the maternity records. In addition, NTD birth statistics were later collected from Onandjokwe Hospital records from September 2018 to August 2019 to see if seasonal variation could again be observed.

3.6. DATA COLLECTION PROCEDURE

Interviews were conducted in the hospitals after delivery in a separate room to ensure privacy by the researcher or research assistant, who personally recorded the responses. Sometimes, a nurse is present to serve as an interpreter for the researcher. The names of the participants were omitted from the questionnaires to ensure confidentiality and anonymity only the hospital numbers were used for research purposes which only the researcher had access to. Names on the blood samples were retained because, for accurate identifications, the results could contribute to treatment. No voice recorder was used. The participant was pre counselled. Data was initially captured on the questionnaire then put in an envelope which was then sealed and kept by the researcher in a locked cabinet which only the researcher had access to. No photocopy of the document was done.

Venipuncture was used to collect approximately 3 to 5 ml of blood samples from the participants (cases and control) in the post-natal ward by the researcher or research assistant, following universal precautions and putting it in a sealed ethylenediametetraacetic acid (EDTA) tube. The samples were immediately taken to the Namibia Institute of Pathology (NIP) laboratory staff for processing. Standards laboratory protocols were followed for storage, transportation, analysis and calculation of red blood cell folate.

The maternity records were reviewed in order to capture additional data such as height, weight and haemoglobin. The maternity records at Onandjokwe hospital were also retrospectively reviewed in June 2020, to identify NTD babies born from September 2018 to August 2019, and compared with the September 2016 to August 2017 study results. The main emphasis was put on seasonal variation aspect.

3.7. VALIDITY AND RELIABILITY

Research instruments need to comply with two important requirements, namely; validity (accuracy) and reliability (precision). The term *validity* refers to the extent to which a research instrument actually (accurately) measures what it is meant to measure (Joubert et al., 2007: 117). There are various concepts (types) that explain ways to improve and assess validity of the research instruments: a) Face validity, content validity, criterion-related validity, predictive validity and inconsistent validity. In this study, the researcher applied mainly two types of validity: content and face validity.

According to Hulley, et al. (2007:39) and Brink, et al. (2012: 166) content validity is a way of assessing how well the instrument represents all the elements of the variable or concept being investigated. If one or more elements are neglected, the researcher may not claim to have measured whatever was the focus of the study. Thus, in this study, the research questionnaire reflected both independent and dependent variables, namely: questions on the risk factors and the incidence of NTDs. The researcher has presented the questionnaires to the supervisors, faculty staff and some hospital personnel (mainly doctors) for their input on the representativeness of the listed variables and suitability for use. To assess the accuracy (clarity) and emotional impact of the instrument, a pilot study was carried out prior to the actual data collection on participants with similar characteristics to the sample.

In terms of face validity, Joubert et al., (2007: 117) and Brink, et al. (2012: 166) describe it as a way of assessing whether the instrument makes sense to experts in the field and those familiar with the language and culture of the participants. The researcher submitted the questionnaire to the supervisors, faculty staff and some hospital personnel to evaluate its readability and clarity of the content. The concept of reliability (precision) refers to the degree to which the instrument can be depended upon to produce consistent results if used repeatedly over time by the same person or if used by other researchers (Brink, et al., 2012: 169). In improving and evaluating reliability, there are three aspects that are commonly evaluated, namely stability, internal consistency and equivalence reliability. Stability entails assessing the research instrument consistency over time, measured by giving the same individuals an instrument on two occasions within a relatively short period and examining the responses for similarities (Brink, et al., 2012: 171). In this study, the stability of the

instrument's consistency was not used because participants were only interviewed once within 12 months.

In assessing reliability, Brink, et al. (2012), refer to internal consistency, which is the extent to which all items on an instrument measure the same variable. This type of reliability is appropriate only when the instrument is examining one concept at a time. The researcher found this approach suitable since the study focused on the incidence of NTDs and its risk factors, and all questions in the instrument aimed to measure issues related to NTDs. Equivalence reliability tries to establish whether similar tests given simultaneously produce the same results, or whether the same outcome can be obtained by using different observers at the same time (Brink, et al., 2012). Therefore, reliability in this study was ensured by the same questionnaire administered by different researchers to two groups at separate hospitals to collect data over a period of 12 months.

3.8. DATA ANALYSIS

The term data analysis involves contrasting and comparing the final data to determine which patterns or themes emerge (Brink, et al., 2012: 122). Statistical analysis was applied to analyse the quantitative data within the completed questionnaires. Quantitative data was entered into an electronic database and analysed using the Epi Info. Descriptive statistical analysis was used to describe the magnitude and trend of the NTDs. The data was presented as tables, graphs, charts and maps. Categorical variables were compared using a Pearson chi-square test. A comparison of quantitative variables was performed using the t-test. Analytical epidemiology was used to estimate the risk of NTD. The logistic regression was

used to determine factors associated with neural tube defects. Separate logistic regression analysis was performed for each type of neural tube defect. Logistic regression was chosen because each neural tube defect was expressed as binary in terms of presence or absence.

The dependent variables were the neural tube defects (Spina bifida, Anencephaly, Encephaloceles, Hydranencephaly, and Iniencephaly), while the independent variables were potential risk factors such as socio-demographic characteristics - blood folate concentration and folic acid deficiency. Other variables were maternal obesity, hyperthermia, radiation, maternal smoking and consanguinity; drug use (Valproic acid, Carbamazepine), region, employment and educational level, rural and urban, age, gravidity, gestation, parity, HIV status, body mass index (BMI) and low hemoglobin.

The Odds Ratios, 95% confidence intervals, estimated the relative risk and p-values were computed. Bivariate analysis was performed first and all variables with p-values less than 0.2 were entered in the multivariate analysis model. A manual forward stepwise procedure was applied. In all analyses, a p-value of less than 0.05 was considered statistically significant and Epi-info software was used in all analyse. The statistician was consulted to assist with the suggested statistical tests.

3.9. RESEARCH ETHICAL CONSIDERATIONS

Research studies are expected to adhere to basic ethical principles that are general judgements that serve as a basic justification for human actions and for protection of participants (Joubert et al., 2007: 30). There are three basic principles that are relevant to healthcare (medical) ethics involving human subjects, namely: a) respect

for persons, b) beneficence and c) justice. According to Joubert et al. (2007: 30), respect for persons refers to individuals' autonomy and the right to voluntarily participate in the study. Participants were informed that participation was voluntary and that they had the right to withdraw from the research if they did not want to continue, without any explanation or consequences to themselves. The researcher disclosed information about the research fully in both English and Oshiwambo. Because participants were adults, written consent was obtained (annexures F and G) before completing the questionnaire and collecting blood samples from them. In this study, separate written consent was not deemed necessary for examination because it formed part of the normal patient clinical care of the babies.

In addition, approval to conduct the study for research purposes was obtained from the Research Committee of the Faculty of Health Sciences, School of Medicine of the University of Namibia (UNAM) prior to the commencement of the study (annexure B). The ethical clearance was also obtained from the Ministry of Health and Social Services (MoHSS) prior to the commencement of the study, annexure C. Participants were provided with information relating to ethical research, written in a language they understood, which was either English or Oshiwambo. Confidentiality was assured since only the researcher had access to the information that will be collected. The use of respondents' names was avoided. Respondents were at liberty to use a language of their choice as much as possible.

Regarding beneficence and non-maleficence, it is expected that the benefit of scientific knowledge gained from the research should not be at the expenses of participants' physical and psychological wellbeing (Hulley et al. 2007: 210).

In this study, all respondents were assured that confidentiality would be maintained, no identity and names were mentioned and the researcher was the only one who kept the documents in a locked cabinet at UNAM. The researcher provided pre-counselling to participants before the questionnaires were administered. Inclusion and exclusion criteria were applied to participants who were likely to suffer harm, for example vulnerable groups such as minors, mentally retarded individuals and minors. In terms of justice, it is required that benefits and burdens of research be shared fairly among the population and be treated equally (Hulley et al., 2007: 210; Joubert et al., 2007: 33). Legal guardians could give consent for minors and vulnerable persons should there be a compelling need.

The researcher focused on all mothers with and without NTD babies without specifying any particular group or location. The researcher administered a structured questionnaire to each mother with NTDs and interviews were conducted face to face by the researcher. Arrangements were made with the hospital medical superintendents, the hospital nurse managers at Oshakati and Onandjokwe hospitals.

3.10. SUMMARY

This chapter discussed the research design and methods, the population and sample selection used in the study. The processes for collecting data, as well as the reasons for using the mixed method approach, were described. Data analysis for both approaches was described. Validity and reliability were discussed. The application of ethical principles in the study was explained. The next chapter presents the findings of the study.

CHAPTER FOUR: RESULTS

4.1. INTRODUCTION

This chapter presented the results derived from data relating to and in line with the main objectives of the study in terms of the incidence of NTDs, seasonal variations (monthly) and risks factors. The chapter stated key findings, and proposed the development of interventions to address NTDs in Northern regions of Namibia. Any discrepancies observed in the denominators (risk factors and BMI, etc.) is a consequence of some missing data. The results were presented as numbers, percentages, ratios, tables, graphs and descriptions.

4.2. DETERMINATION OF INCIDENCE OF NTDs PER 10000 BIRTHS

In this section, the results on NTDs were presented according to the distribution of cases and type per hospital, the combined cases of all hospitals and by region as well as demography factors e.g. by age and BMI of all mothers in cases and controls. The study found that the combined incidence of neural tube defects was 11 per 10000 births for Oshakati and Onandjokwe Hospitals. This was calculated as follows: six neural tube defect affected babies were born in Oshakati hospital per 7082 births over 12 months, which is equivalent to 8 per 10000 births. Nine neural tube defect affected babies were born in Onandjokwe hospital per 6996 births over 12 months, which is equivalent to 13 per 10000 births. The combined number of cases of NTDs affected babies was 15 out of 14078 births born in Oshakati and Onandjokwe hospitals over 12 months from September 2016 to August 2017, equivalent to an incidence of 11 per 10000 births.

Table 8 below presents the type of NTDs per hospital and percentage for the combined hospitals. Hydranencephaly was the most common type with 67% at Onandjokwe and 67% at Oshakati, while Spina bifida was 33% at Onandjokwe and 33% at Oshakati respectively.

Table 8: The distribution of type of NTDs per hospital

HOSPITAL	NTDs	NTD TYPE	NUMBER OF CASES	PERCENTAGE %
Onandjokwe	9	hydranencephaly	6	67
		spina bifida	3	33
Oshakati	6	hydranencephaly	4	67
		spina bifida	2	33
TOTAL	15	hydranencephaly	10	67
		spina bifida	5	33

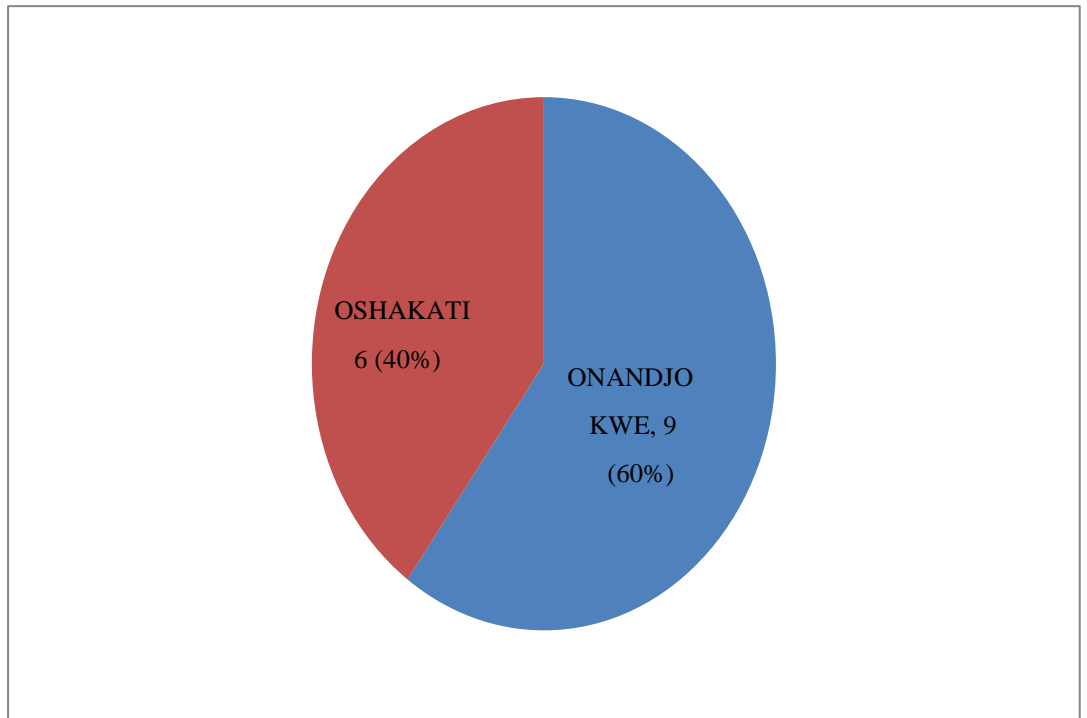


Figure 4. NTD Cases per Hospital

The majority of cases (60%) were delivered at Onandjokwe hospital in comparison with Oshakati.

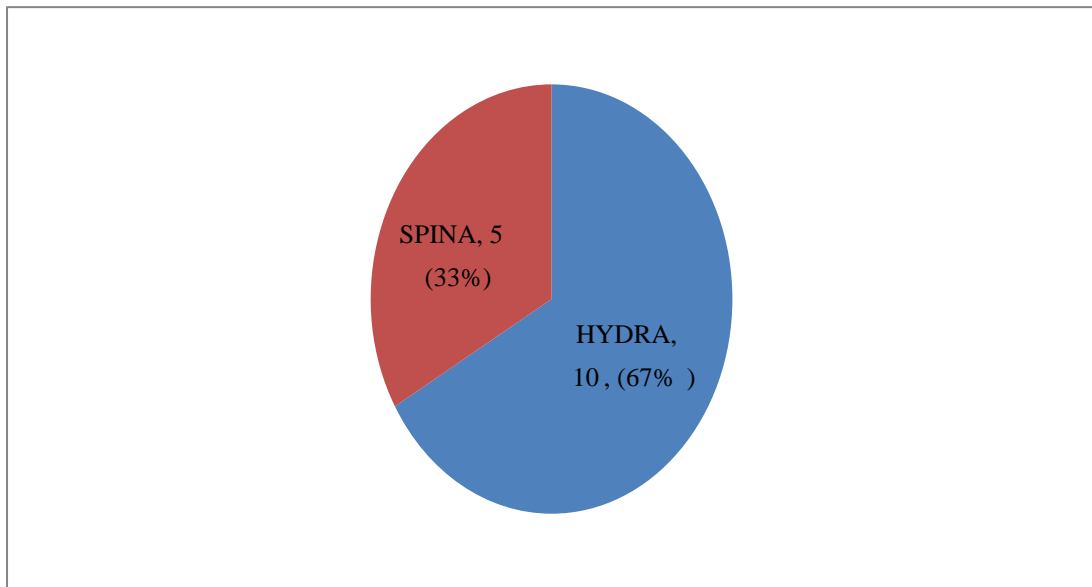


Figure 5. Types of NTDs

From the two combined hospitals, this study found two types of NTDs: 10 out of 15 cases were hydranencephaly, representing 67%, while five out of 15 cases were

spina bifida, representing 33%. Mild cases of neural tube defects such as spina bifida occulta might have been missed in the study because it is difficult to diagnose them clinically.

Table 9: The distribution of cases of neural tube defects by region

REGIONS	NTD CASES	PERCENTAGE %
Oshikoto	7	47
Ohangwena	3	20
Oshana	5	33
TOTAL	15	100

The majority of cases, 7, (47%) came from Oshikoto region in comparison to Oshana and Ohangwena.

4.3. SEASONAL VARIATION IN BIRTH OF BABIES WITH NTDs

This section presented a relationship between the conception of babies with NTD and the months/seasons during which they were born. The study found a clear seasonal variation by month in the birth of babies with neural tube defects, which indicated a corresponding variation in conception as presented on the graph below. The monthly rainfall figures were also indicated for the period of conception.

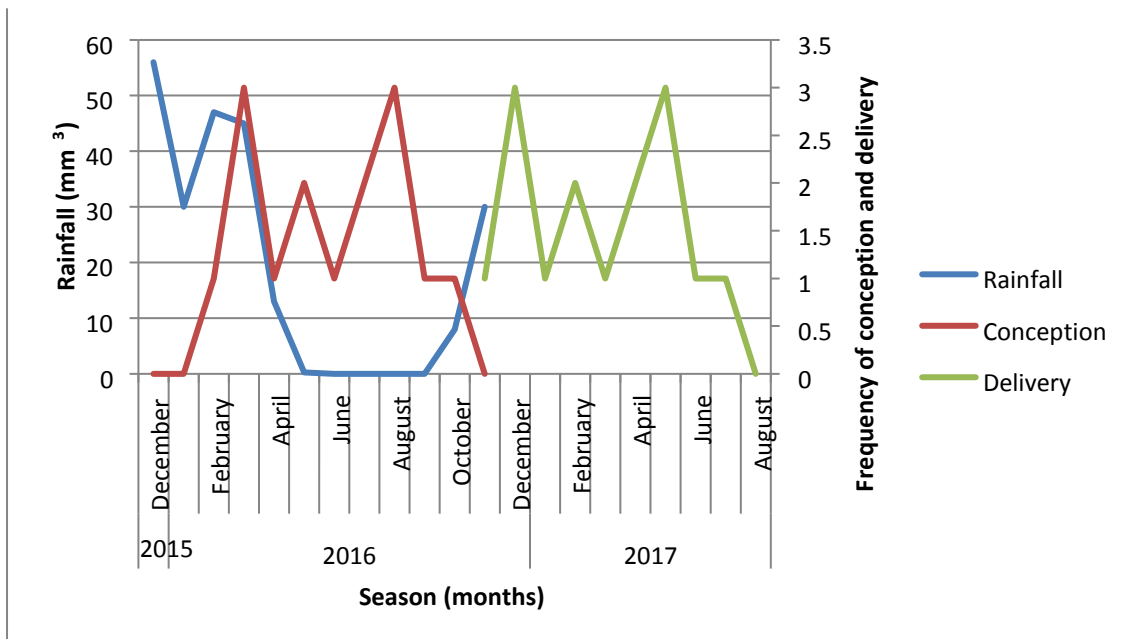
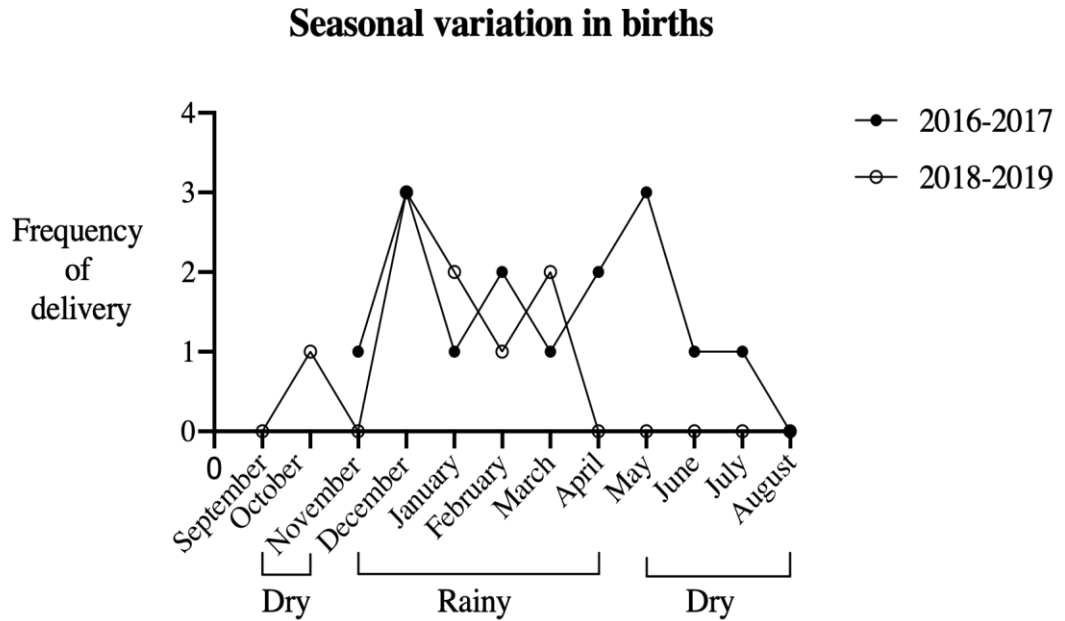


Figure 6. Seasonal variation, conceptions and births of NTD babies in relation to month and rainfall.

In total, 12 babies (80%) were born between December 2016 and May 2017. They were conceived from March 2016 to August 2016, over 6 months, from the end of the rainy season into the dry season. Three babies (20%) were born as follows: one was born during the period of September 2016 to November 2016.

Conception occurred during the period between December 2015 and February 2016. This corresponds to the rainy season. Two were born during the period of June 2017 to August 2017. Conception occurred from September 2016 to November 2016. This corresponds to the beginning of the rainy season. In this study, all babies were born at term. Should a baby be born before term, it may affect the month of delivery but not the month of conception, hence, the main findings will remain the same. The

graph of birth statistics of NTD babies in Onandjokwe hospital from September 2018 to August 2019, again shows a seasonal variation in line with rainfall pattern described by Awala et al (2019).



Eight out of nine NTD babies were born between December 2018 and March 2019 in Onandjokwe Hospital

Figure 7. Seasonal variations in births

According to Awala et al. (2019), based on rainfall data over 30 years, the rainy season start from November to April while the dry season starts from May to October, as indicated in the Figure 7.

4.4. MEAN POSTPARTUM MATERNAL RED BLOOD CELL FOLATE IN CASES AND CONTROLS

In this section, the study presented the maternal postpartum red blood cell folate in participants (mothers) with and without neural tube defect babies according to the type of NTDs at the two hospitals, Oshakati and Onandjokwe. The folate values were measured in both groups; cases and controls to compare with the minimum reference value of 906nmol per litre referred to by Crider et al. (2014), page one of this study.

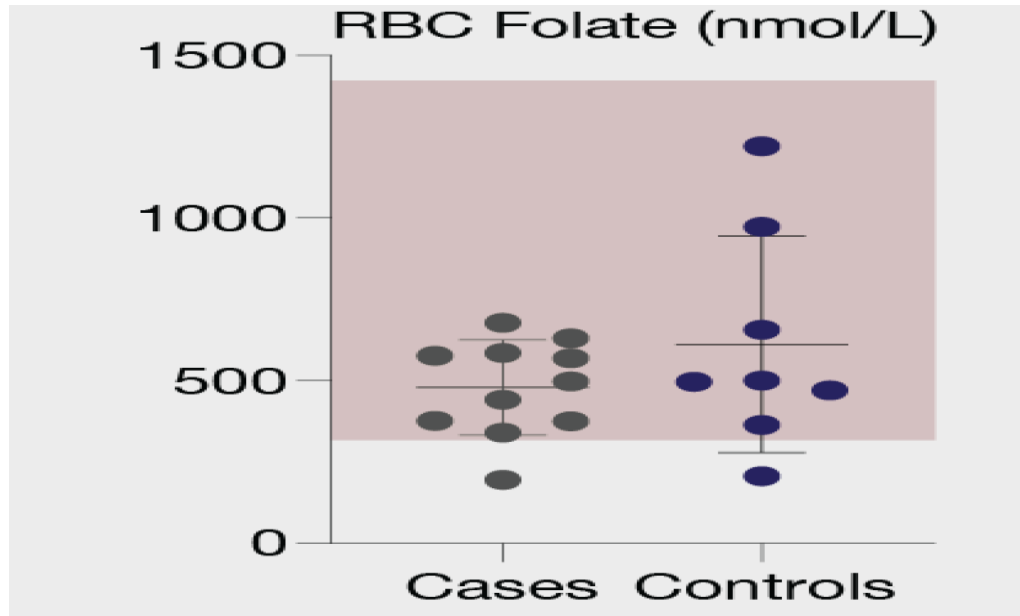


Figure 8. Mean postpartum red blood cell folate

Mean for cases 479 nmol/L; Mean for controls 611 nmol/L; P value 0.2529; 95% confidence interval: -103.8 to 368.0

Most mothers from both groups (cases and controls) attended antenatal care and received folate tablets from the two hospitals. Figure 8 above presents the relationship between postpartum red blood cell folate values and the types of NTDs.

Mean postpartum red blood cell folate for cases was 479 nmol/L and 611 nmol/L for controls. There was no statistically significant difference in the mean RBC folate values between cases and controls.

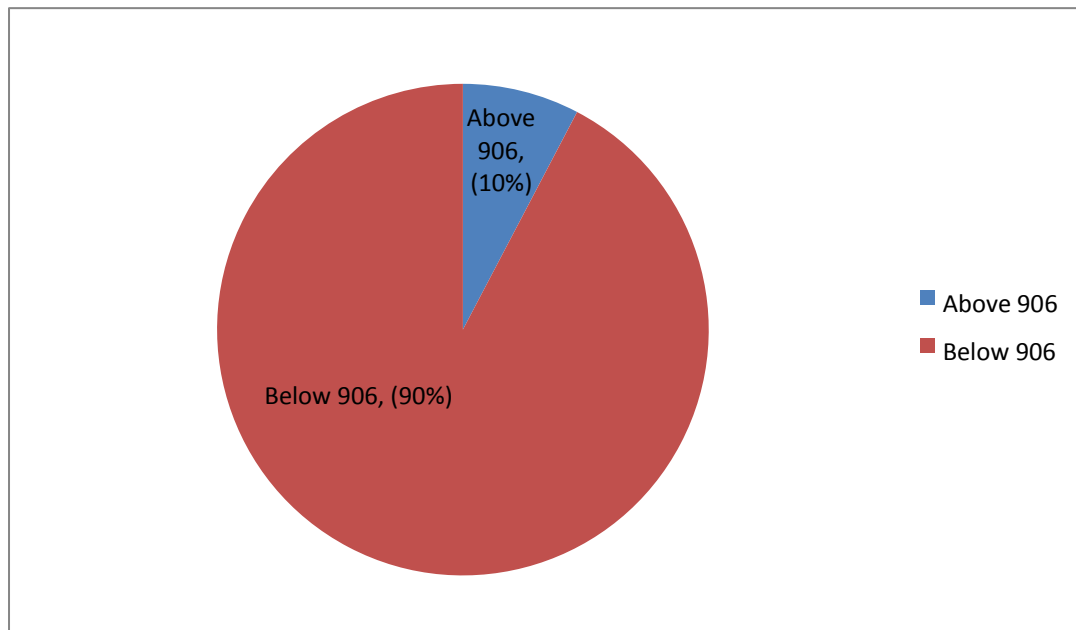


Figure 9. Values of red blood folate among cases and controls.

Seventeen out of 19 (90%) of the mothers (cases and controls) had red blood folate below 906 nmol per liter. In terms of cases, only 11 out of 15 mothers with NTD babies had blood samples taken for postpartum red blood cell folate levels and the results received from the laboratory. One out of 15 did not have a blood sample taken; whereas three mothers had blood samples taken but no results could be found. In controls, nine out of 15 mothers whose babies did not have NTDs had blood samples taken and only eight received results from the laboratory, while six mothers did not have blood samples taken. It was observed that the levels were similar in both groups and were mostly very low compared to the desired periconceptional levels of 906 nmol per litre or more as presented in figure 10 below.

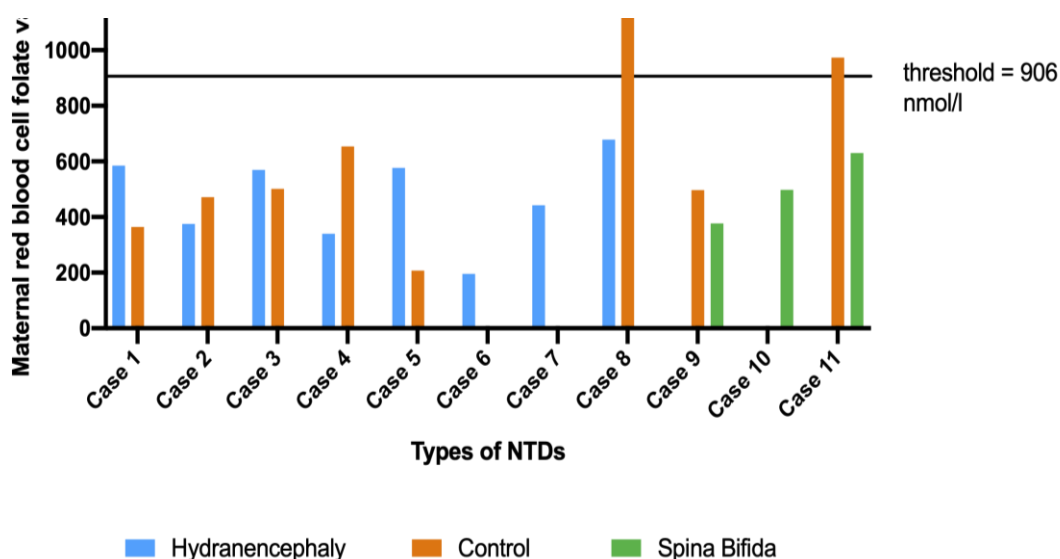


Figure 10. Maternal postpartum red blood cell folate value per type of NTD

Figure 10 above shows the maternal postpartum red blood cell folate values/levels plotted against the type of neural tube defects for both cases. Of the 11 cases, eight had hydranencephaly and three had spina bifida, which were available for analysis. Only eight controls were available for analysis. Red blood cell folate values obtained were mostly below 906 nmol (196 – 678), with the exception of two results (973 and 1221 nmol/l), both in the control group.

4.5. OTHER RISK FACTORS

This subsection presented the results related to other risk factors of neural tube defects. The term risk factors refer to conditions that may contribute to the development of NTDs among babies, as described in the literatures (Salih et al., 2014b). Risk factors are delineated as follows: socioeconomic status (education and work, diet, smoking, alcohol consumption, marital status and consanguinity); health related conditions (diabetes, antiepileptic drugs, exposure to radiotherapy, exposure to extreme temperature); red blood cell folate levels and recurrent NTDs.

Postpartum red blood cell folate results were already presented. The results of other risk factors will be presented in line with conditions identified as outlined above.

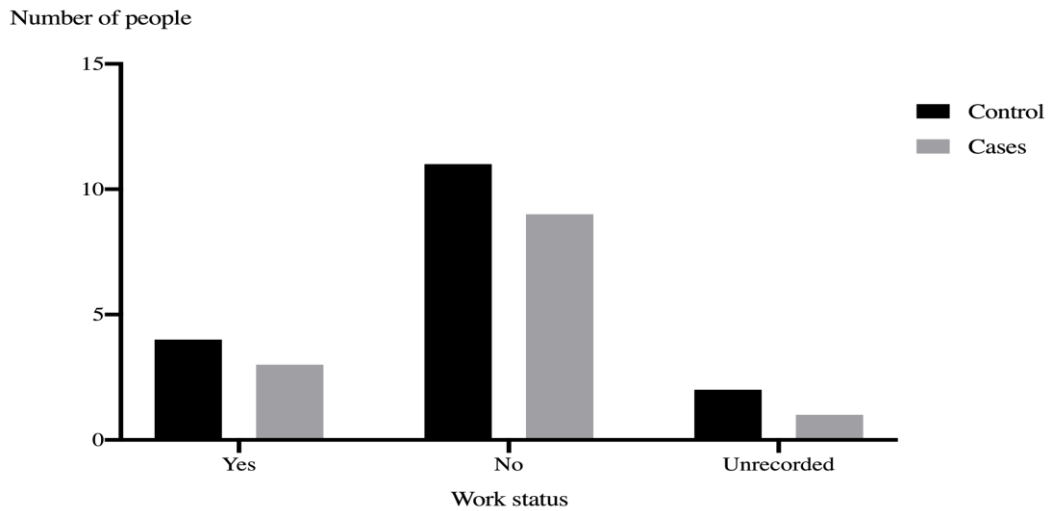


Figure 11. Work Status (OR = 0.6750; CI = 0.1177 – 3.8726; P VALUE = 1.00)

There was no difference in the work status of mothers with and without neural tube defects affected babies. Eleven out of 14 mothers whose babies had NTDs were unemployed (79%), while nine out of 13 mothers whose babies did not have NTDs were also unemployed (69%).

Most mothers whose babies had neural tube defects were either not employed or self-employed (11/14). There was a slightly higher number of unemployed mothers in the cases in comparison to the control group (9/13).

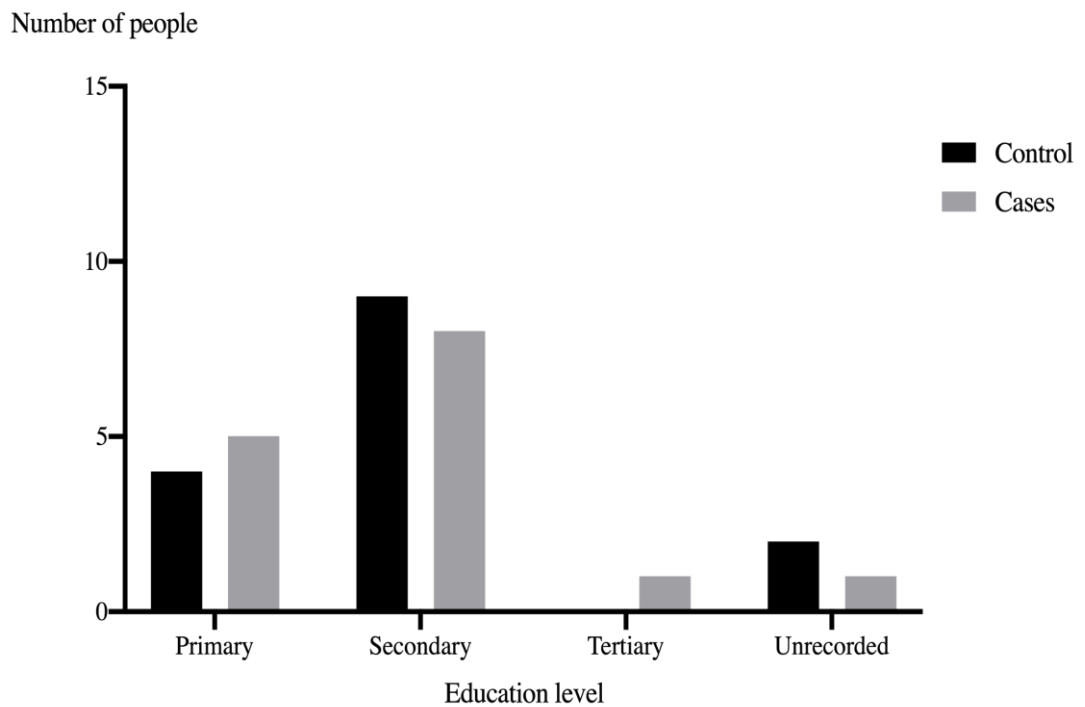


Figure 12. Education level (OR = 1.00; CI = 0.1891 – 5.2893; P VALUE = 0.66)

On the level of education, most mothers in both groups had up to secondary school level education. Five out of 14 mothers whose babies had NTDs had only primary education (36%) and eight out of 14 mothers whose babies had NTDs had secondary education (57%). In terms of controls, nine out of 13 mothers whose babies did not have NTDs had secondary education (69%), while four out of 13 had primary education (31%).

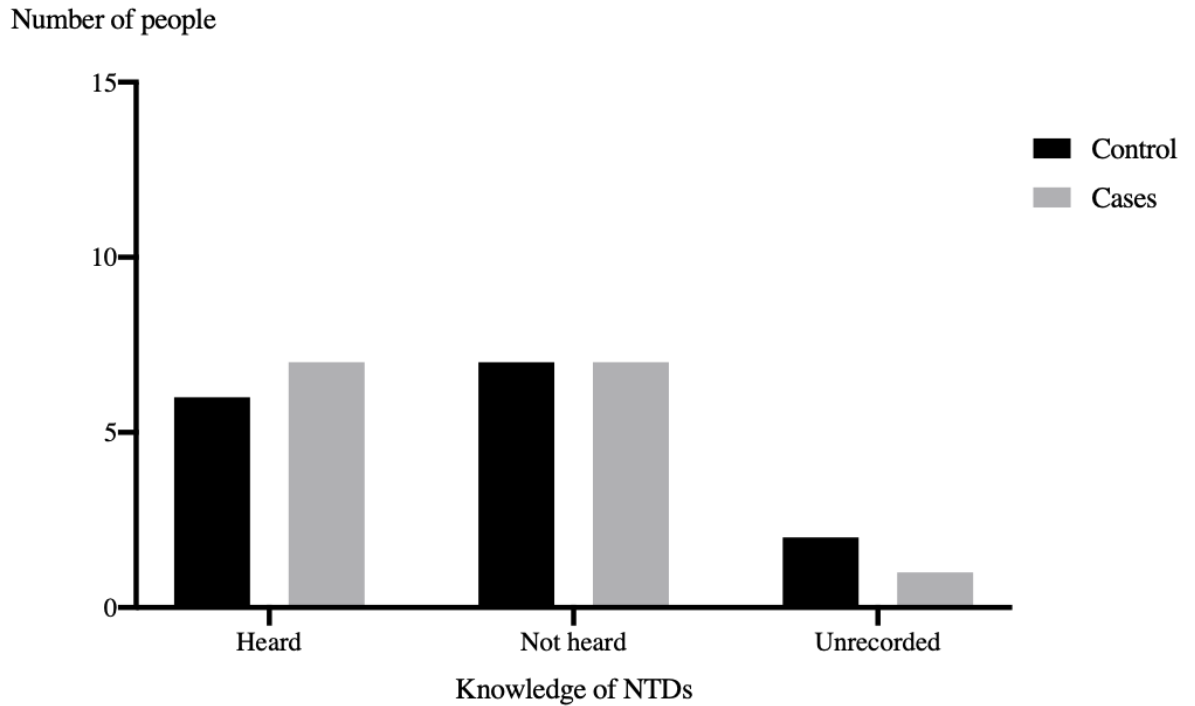


Figure 13. Knowledge of NTDs (Cases 50% know, Controls 54% know, No difference.)

On knowledge of neural tube defects, 7 out of 14 mothers whose babies had NTDs had previously heard of neural tube defects (50%), while 7 out of 14 mothers had not (50%). Six out of 13 mothers whose babies did not have NTDs had heard of NTDs (46%), whereas seven out of 13 had not (54%).

Table 10: Gravity and parity

GRAVIDITY AND PARITY											
Count	1	2	3	4	5	6	7	8	Total	Unrecorded	
Cases (15)	Gravida	4	3	4	1	1	0	0	1	14	1
	Para	4	4	4	1	0	0	0	1	14	1
Controls (15)	Gravida	6	6	0	0	0	1	0	0	13	2
	Para	6	6	0	1	0	0	0	0	13	2

The gravity of all mothers was similar (ranged from one to 8), whereas parity was different in the two groups (cases 1-8) and (controls 1-4), which did not suggest an association with neural tube defects. No stillborn babies with and without neural tube defects were found in this study. The two hospitals also did not conduct early termination of pregnancies with neural tube defect babies.

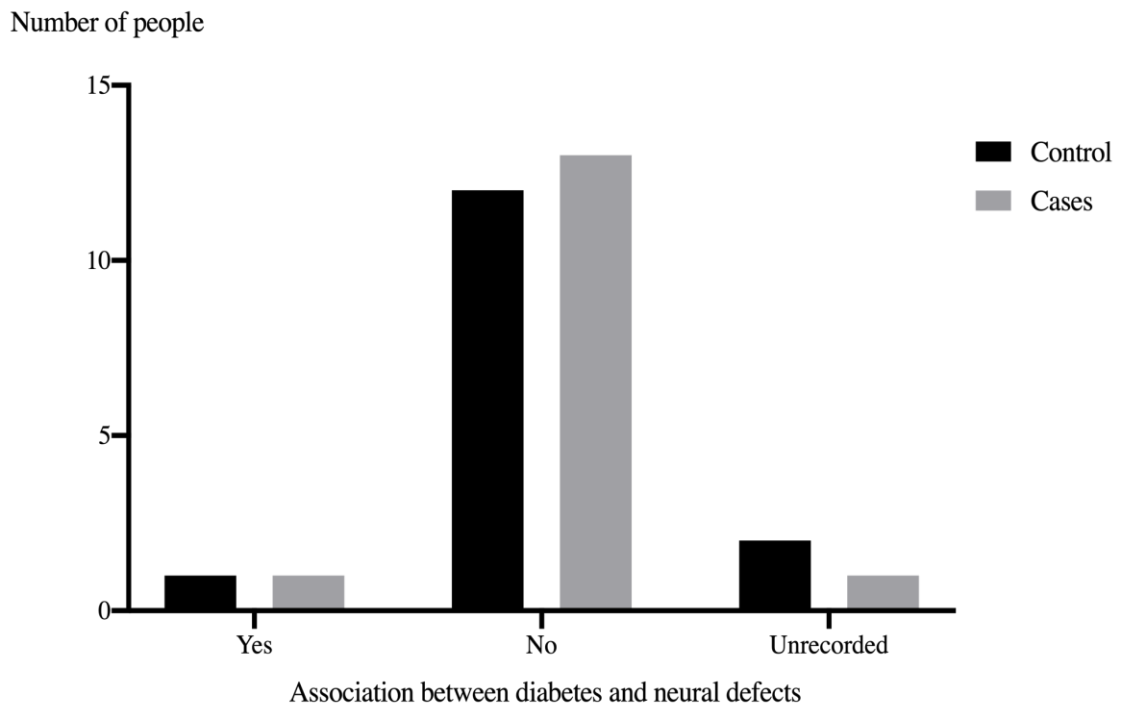


Figure 14. Diabetes and neural defects

Odds Ratio = 1; 95% Confidence interval (0.0559 - 17.9043); p-value = 1

The 95% Confidence interval is wide, which means the sample size was small. Thirteen out of 14 mothers with neural tube defects affected babies were not diabetic. Therefore, there was no difference in the odds of giving birth to a baby with a neural defect among cases and controls. While Reece, (2012) reported that congenital abnormalities were common in babies born by diabetic mothers, in this study one out of 14 mothers with NTDs affected baby was diabetic.

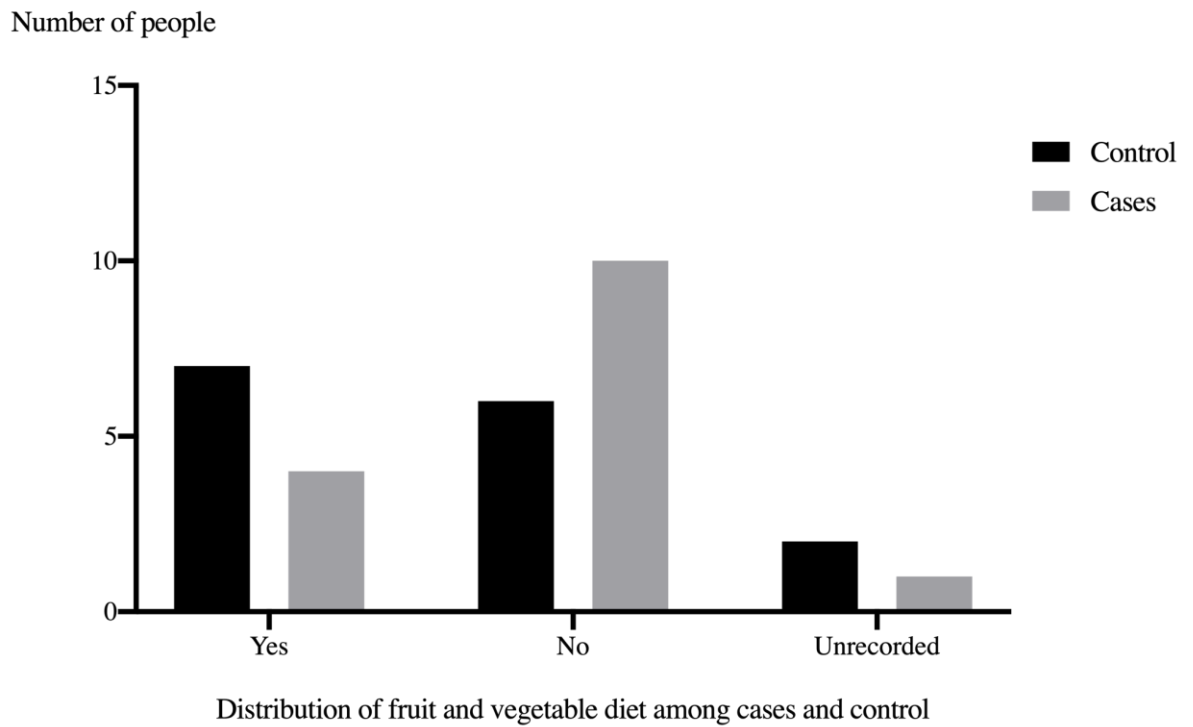


Figure 15. Distribution of fruit and vegetable diet among cases and control
 Odds Ratio = 0.38; 95% Confidence interval (0.0765 - 1.8965); p-value = 0.23

The probability of giving birth to a baby with neural tube defects among mothers who ate fruit and vegetables was lower than those who did not eat fruit and vegetables. However, the findings were not statistically significant because the 95% Confidence interval includes one. Most mothers whose babies were affected by neural tube defects (10 out of 14) rarely consumed fruit and vegetables.

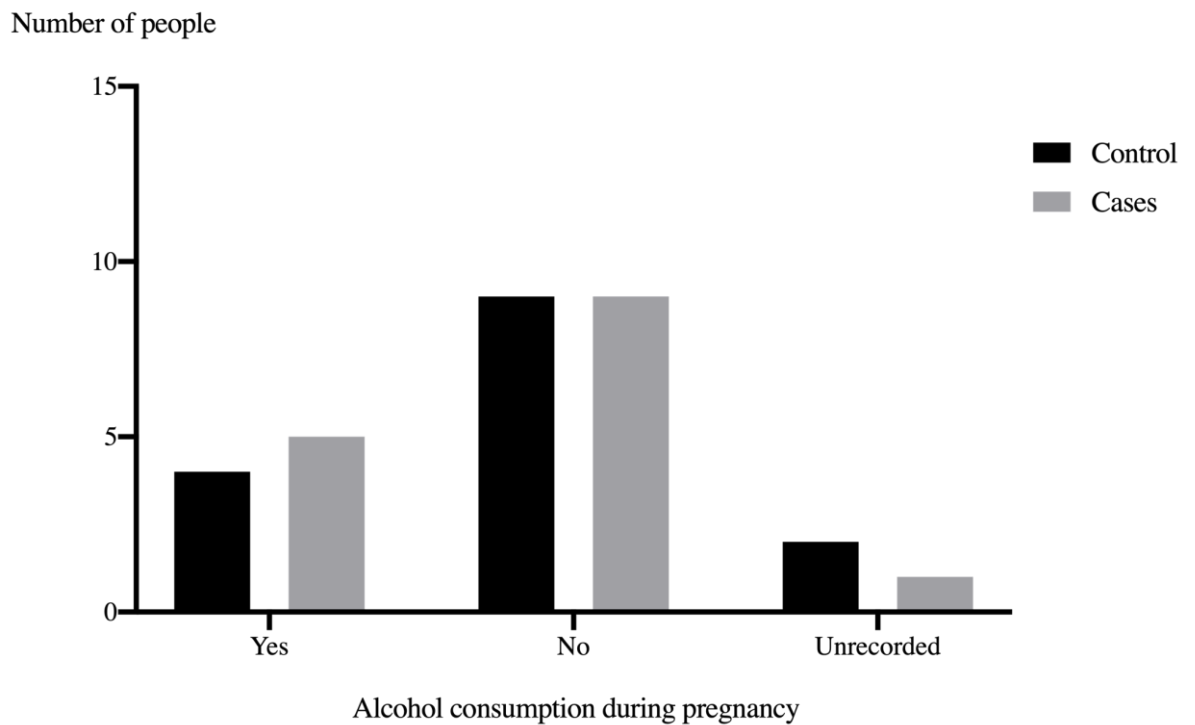


Figure 16. Alcohol consumption during pregnancy

Odds Ratio = 1; 95% Confidence interval (0.1891 - 5.2893); p-value = 1

There was no difference in the odds of giving birth to a baby with neural tube defects among cases and controls. Five out of 14 mothers whose babies had NTDs consumed alcohol during pregnancy, while nine did not consume alcohol and one case out of 15 was not recorded. Nine out of 13 mothers whose babies did not have NTDs did not consume alcohol, whereas four consumed alcohol and two mothers out of 15 were unrecorded due to incomplete entry.

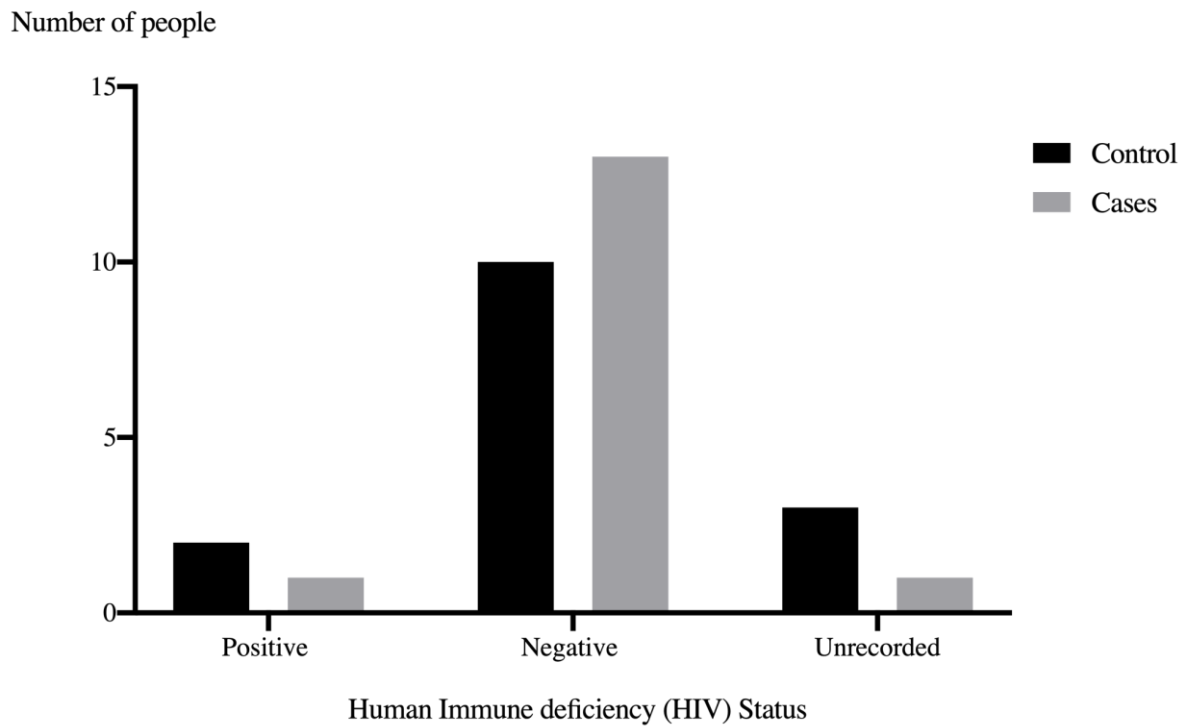


Figure 17. Human Immune Deficiency Virus (HIV) Status

Odds Ratio = 0.45; 95% Confidence interval (0.0363 - 5.7889); p-value = 0.53

These findings are not statistically significant as the 95% Confidence interval includes one. Thirteen out of 14 cases of mothers with neural tube defects affected babies tested negative for HIV, while one was not recorded. Ten out of 12 controls of mothers whose babies did not have NTDs tested negative, while three were not recorded.

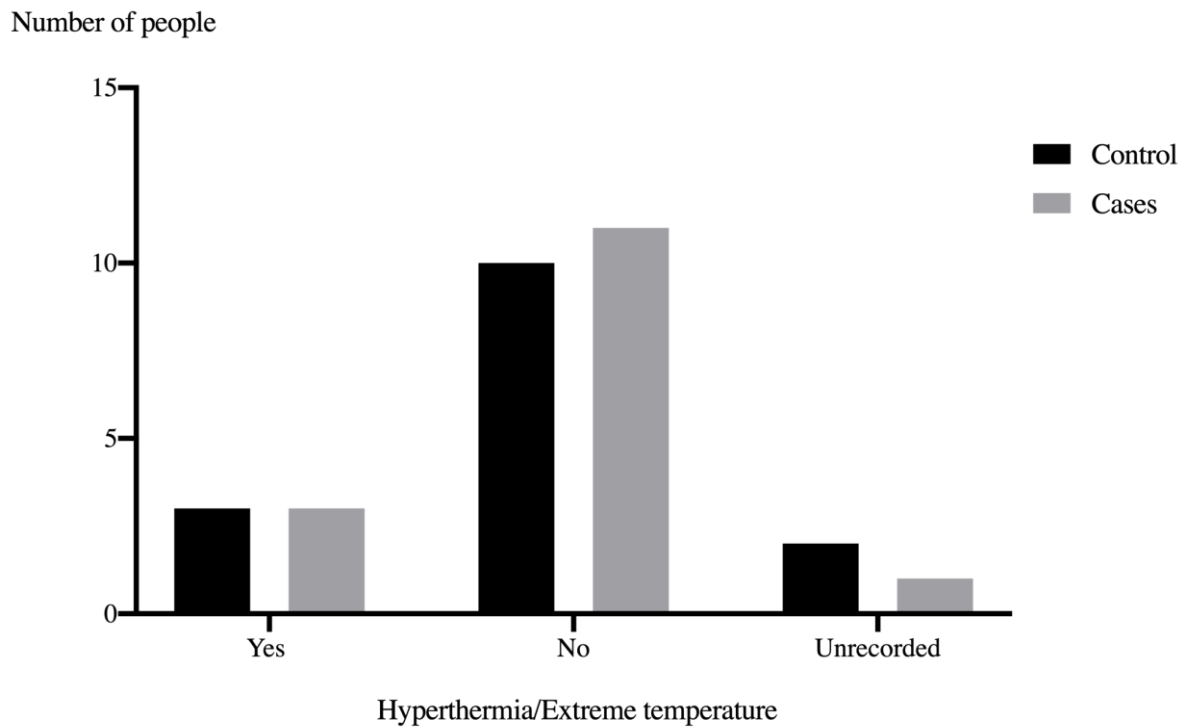


Figure 18. Hyperthermia / Extreme temperature

Odds Ratio = 1; 95% Confidence interval (0.1613 - 6.2007); p-value = 1

Three out of 14 mothers with NTDs affected babies said they were exposed to hyperthermia, (either fever or exposure to hot environmental temperature) while 3 out of 13 mothers whose babies did not have NTDs reported any exposure to hyperthermia. The details of the exposure were not clarified. Since the numbers were small, the significance of this finding could not be established, and the proportions were similar in the cases and controls. There was no difference on the odds of giving birth to a baby with neural tube defect among cases and controls due to exposure to high temperature. Regarding radiotherapy, one out of 14 mothers whose babies had NTD was reported to have been exposed to radiotherapy, while no mother in the control group was exposed.

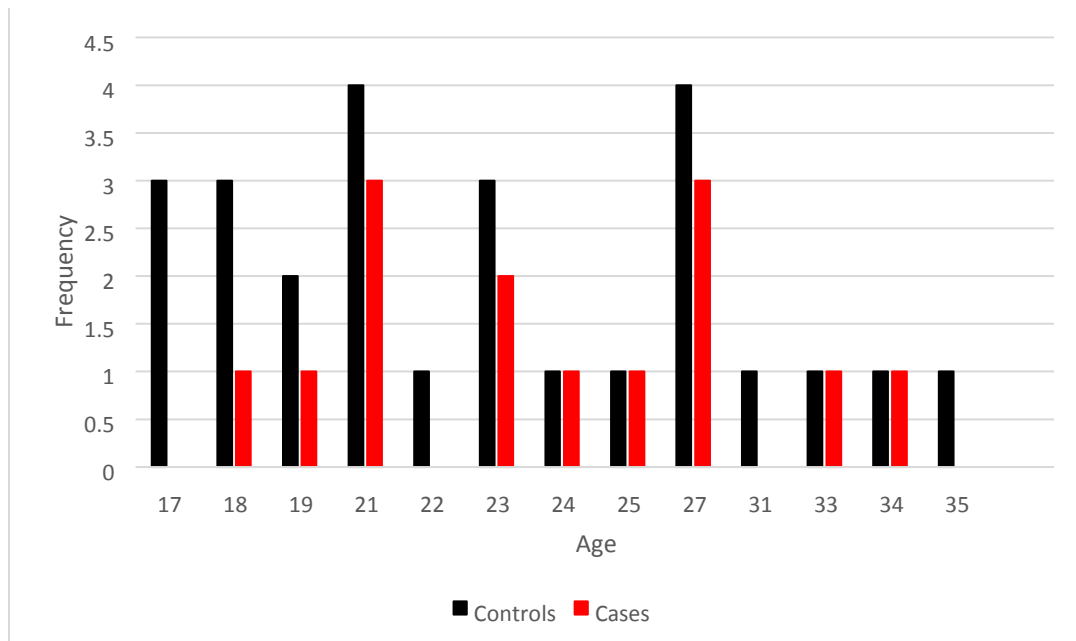


Figure 19. Age distribution for the cases and controls

The mean age of mothers who gave birth to babies affected by neural tube defects (cases) was 25 years, while the range was from 18 to 34 years. The mean age of mothers who gave birth to babies without neural tube defects (controls) was 22 years, while the range was 17 to 35 years. The finding on the mean ages was that the mothers in the control group were slightly younger, (22 years).

Obesity

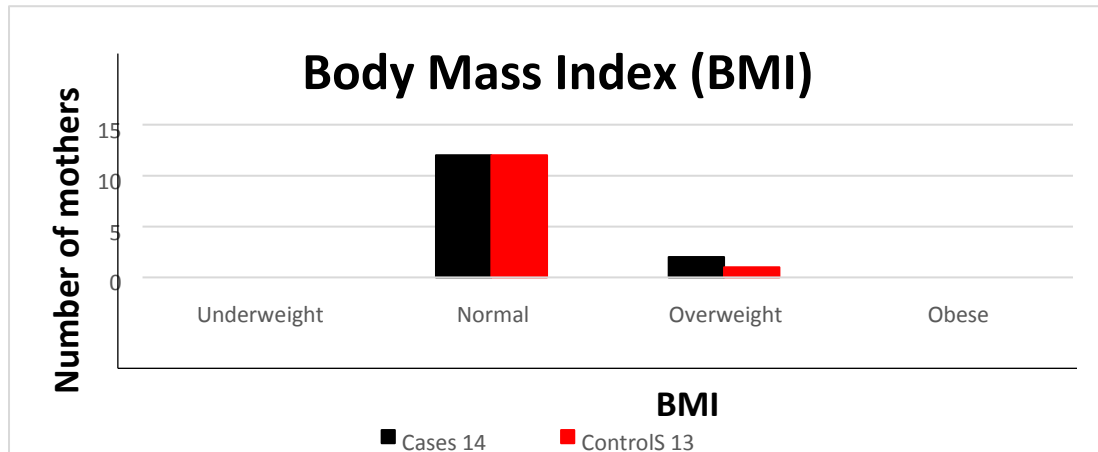


Figure 20. Body Mass Index (BMI) of mothers with and without neural tube defect (NTD) babies.

This graph presented the body mass indices (BMI) of mothers of babies with and without neural tube defects under the following categories: underweight (BMI less than 19), normal (19 -24), overweight (25 -29) and obese (30 and more). The BMI is a person's weight in kilograms divided by the square of the height in meters. In this study, 15 mothers with and without NTD-affected babies participated, but only 14 cases and 13 controls were recorded due to missing values. None of the mothers fell in the obese category and the findings were similar in both cases and controls.

Furthermore, in terms of cases, the mean height of mothers whose babies were affected by neural tube defects was 1.6 meters, while the range was from 1.5 to 1.7 meters. The mean height of mothers whose babies were born without neural tube defects (controls) was 1.6 meters, while the range was from 1.5 to 1.70 meters. The mean weight of mothers whose babies were affected by neural tube defects was 59 kilograms, while the range was from 44.6 to 80.0 kilograms. The mean weight of mothers whose babies were born without neural tube defects was 56 kilograms,

while the range was from 47 to 69 kilograms. The mean BMI for mothers whose babies were affected by neural tube defects was 23, while the range was 20 – 28. The mean BMI for mothers of babies born without neural tube defects was 22, while the range was 20 – 27. Therefore, none of the mothers from both groups fell in the underweight category, which is BMI lower than 19.

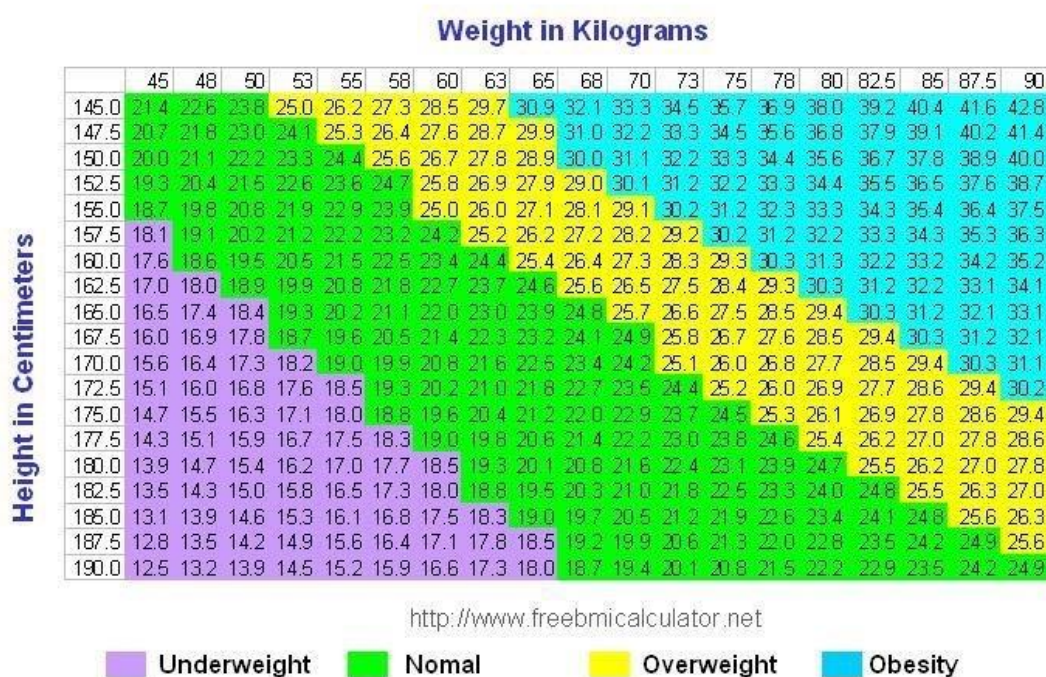
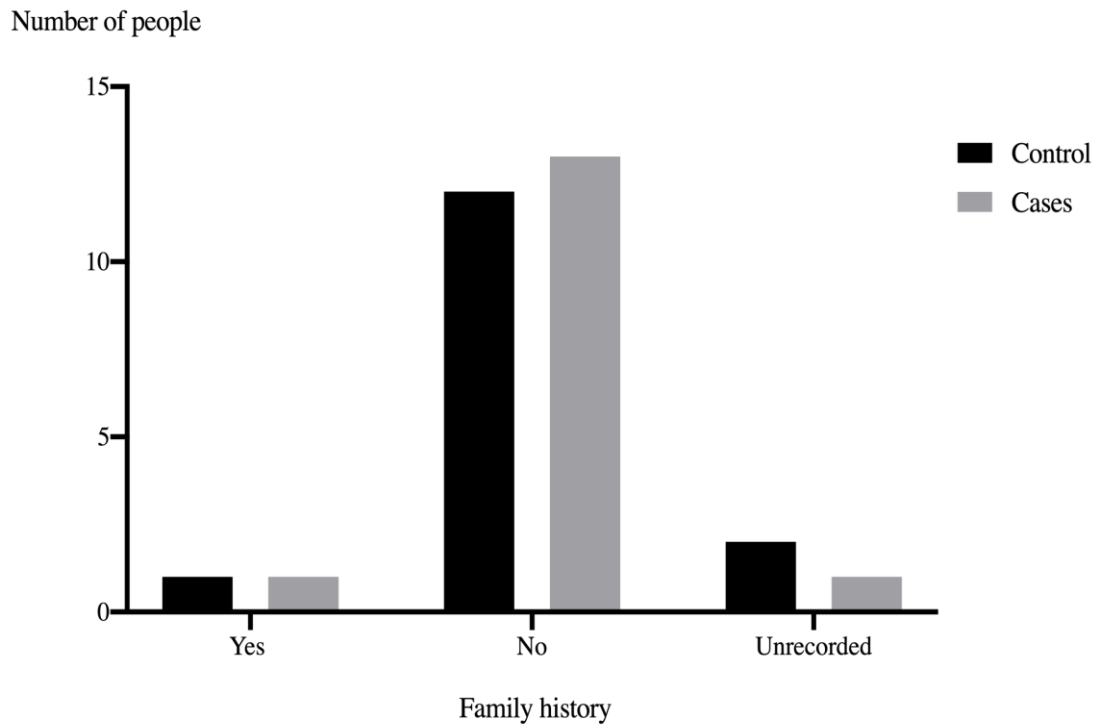


Figure 21. BMI can be calculated as shown in the chart above.

Source: (<https://www.freebmi-calculator.net/bmi-chart.php>.)

Using the chart above, 12 out of 14 mothers with NTD-affected babies had BMI in the range between 19 and 24, putting them in the normal category (86%). Two out of 14 mothers whose babies had NTDs had a BMI between 25 and 29, putting them in the overweight category (14%). In terms of controls, 12 out of 13 mothers without NTD-affected babies had a BMI between 19 and 24, putting them in the normal

category (92%). One out of 13 mothers whose babies did not have NTDs babies had BMI in the range between 25 and 29, putting her in the overweight category (8%).

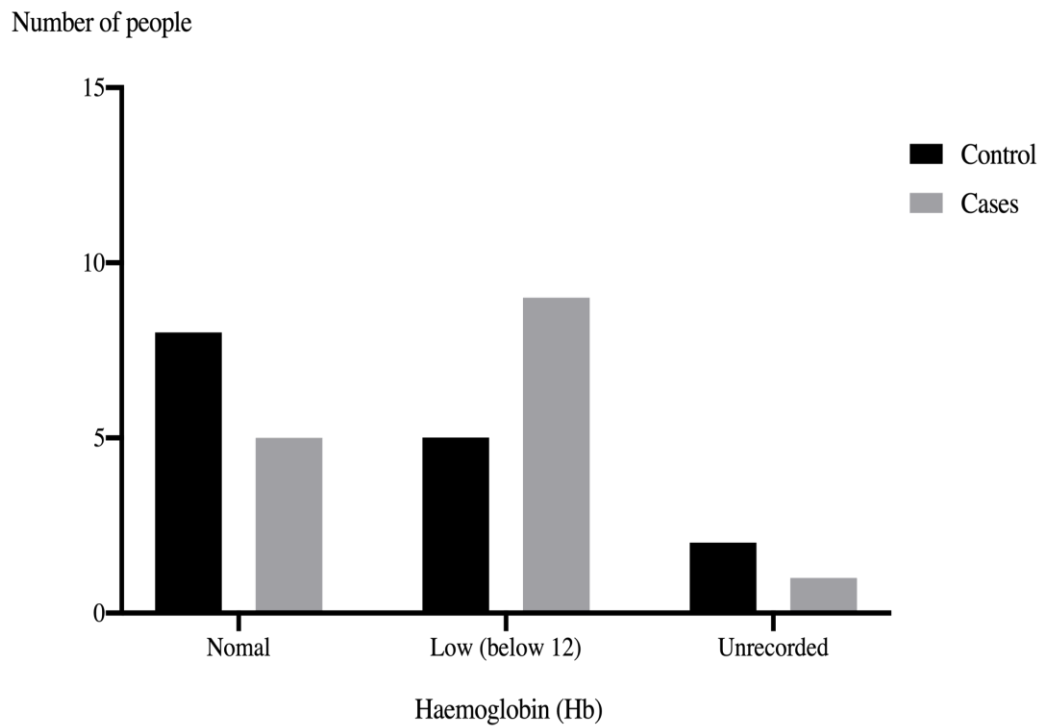


Odds Ratio =1;

Figure 22. Family history

Confidence interval (0.0559 - 17.9043); p-value = 1

There was no difference in the odds of giving birth to a baby with neural tube defects between the cases and control groups. However, the 95% Confidence interval is wide, which means the size was small. Only one out of 14 mothers of babies with neural tube defects gave a positive family history of neural tube defects, whilst none of the mothers in this study gave a positive history of recurrent neural tube defects.



Odds Ratio = 2.56;

Figure 23. Haemoglobin (Hb)

Confidence Interval = (0.5272 - 12.4312); p-value = 0.23

The odds of giving birth to a baby with neural defects are 2.6 higher among the women with low haemoglobin as compared to the women with normal haemoglobin. According to the Namibia Institute of Pathology (NIP) Laboratory, the normal haemoglobin (Hb) level for women is between 12 and 16.9 %. In this study, the cases, mothers whose babies had NTDs had mean haemoglobin of 11.4 g/dl, with a range between 11 and 13 %. Nine out of 14 mothers whose babies had NTDs had Hb below 12g/dl (anaemia), while five out of 14 mothers whose babies had NTDs had normal Hb.

In terms of the control group, the mean haemoglobin level of mothers whose babies did not have NTDs was 11.99 g/dl with a range between 9, 2 and 13g/dl. Five out of 13 mothers whose babies did not have NTDs had Hb below 12g/dl (38%), while eight out of 13 mothers had normal Hb 12gg/dl or above, (62%). Clearly, haemoglobin levels did not show striking differences between the two groups, but were slightly lower in the mothers of NTD-affected babies ($p = 0.23$). Nevertheless, low Hb in cases could be related to low postpartum folate, which could indicate high risk for NTDs in the population.

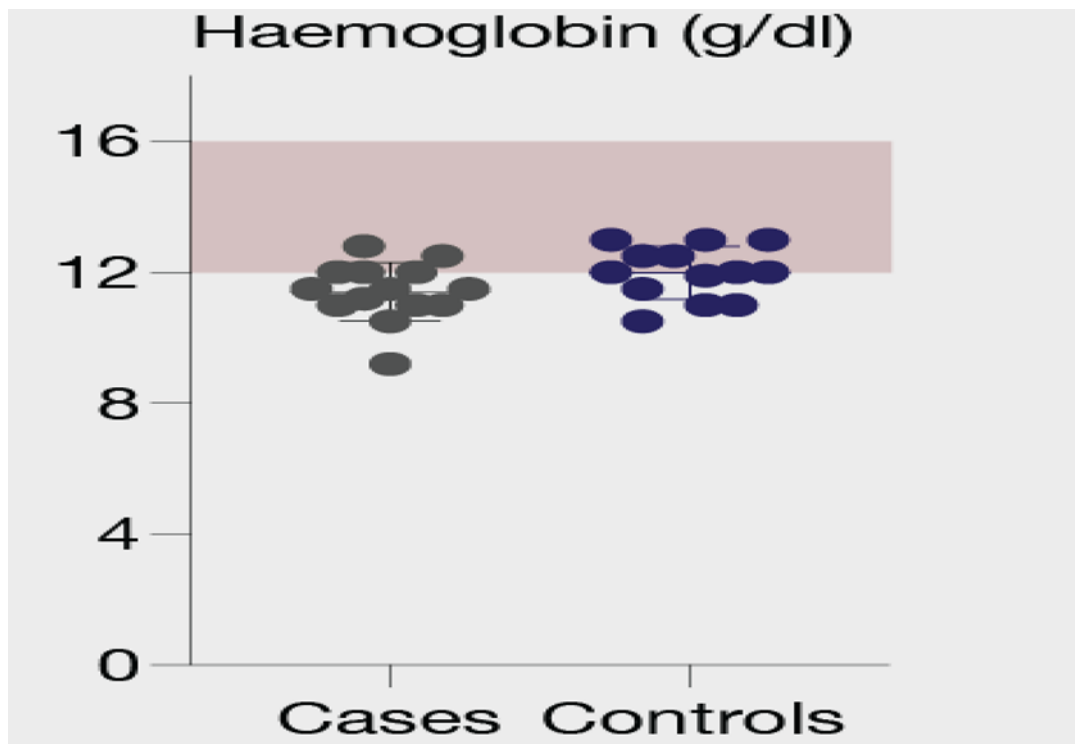


Figure 24. Mean haemoglobin

95% confidence interval: -0.0964 to 1.2; Mean Hb for cases is 11.41 and for controls is 11.99 g/dl; p-value: 0.0893.

Table 11: Percentage anaemia

Hemoglobin value				
	>= 12	< 12	Unrecorded	% anaemia
Cases	5	9	1	64
Controls	8	5	2	38

The percentage of cases with anaemia was 64% while controls were 38%. The main point of interest is that anaemia was observed in both groups. Figure 24 shows the values of haemoglobin for both cases and controls. The majority of cases have anaemia, with a haemoglobin level below 12 g/dl. The normal range of haemoglobin is 12-16 g/dl as indicated in figure 24. The p value is 0.0892, which shows that there is no significance difference between the cases and controls.

Table 12: Radiation exposure, consanguinity, marriage, drugs and smoking

Variable	Cases			Controls		
	Yes	No	Not recorded	Yes	No	Not recorded
Radiation exposure	1	13	1	0	13	2
ANC folate	11	3	1	10	3	2
Consanguinity	0	14	1	0	13	2
Marital status	0	14	1	0	13	2
Drugs	0	14	1	0	13	2
Smoking	0	14	1	0	13	2

The variables in the table above do not appear to be associated with the occurrence of NTDs in this study.

4.6. SUMMARY

The key findings derived from this prospective study can be summarized as follows: It appears that this is the first study to look into the incidence of NTDs in two hospitals in Namibia, which established an incidence of 11 NTDs per 10 000 births. It revealed a seasonal variation, with most NTDs babies conceived during the dry season, and born mostly during the rainy season. It observed anaemia during pregnancy, and low postpartum red blood cell folate in mothers. The study found hydranencephaly to be the most common NTDs in babies. It identified risk factors that were related to the occurrence of NTDs and therefore possibly played a contributory role in the high incidence of NTDs, namely; low postpartum red blood cell folate, anaemia, unemployment, low level of education and knowledge on NTDs, and a diet low in fruits and vegetables. The following risk factors were identified not to be associated with NTD incidence and thus likely to have a minimal effect on NTDs: drugs, radiation, hyperthermia, diabetes, obesity, smoking, HIV exposure, and consanguinity.

CHAPTER FIVE: DISCUSSION

5.1. INTRODUCTION

This chapter presented the discussions and interpretations of the results of the study from the previous chapter. The results of this study were discussed in line with the following objectives:

1. To determine the incidence of NTDs per 10 000 births over 12 months;
2. To determine whether a seasonal variation (by month) exists in the birth of babies with NTDs;
3. To compare mean postpartum maternal red blood cell folate between cases and controls
4. To identify the possible risk factors associated with NTDs babies.

It highlighted the significance of the results, the similarities with and differences from other studies as well as possible limitations of the study. The relative rarity of NTDs were pointed out, and the incompleteness of data collected from a few cases, which reduced the numbers available for analysis. In this study, 15 cases of NTDs per 14078 births were found, which could be categorised as a small number of participants in robust research. However, making a case of research on rare cases, Gagne et al. (2014) and Whicher, Philbin and Aronson, (2018) emphasised that robust and rigorous research can be conducted on rare health conditions despite small numbers of participants. This is because, although individually each rare condition affects a small number in the population, collectively, a large number of individuals are affected. Therefore, delay in conducting research on a small number of rare conditions would result in delayed documentation, treatment and prevention of important conditions. Furthermore, Gagne et al., (2014) defined rare health

conditions based on the statutory definitions set at less than 64 cases per 100,000 people per year in the USA and less than 50 cases per 100, 000 people per year in the European Union (EU). This translates to 60 million people per year. Thus, waiting for the large number of rare cases to be reached per year creates barriers for research to be conducted, the advancement of knowledge, and treatment to be given to the affected people. The IRDiRC report (2016) listed several designs, that include Bayesian design, which takes into account the pre-existing knowledge, to address challenges related to small populations in the field of research on rare conditions. Therefore, the results in this study on rare conditions (NTDs) were interpreted by taking into consideration both the descriptive statistics and the pre-existing knowledge on the subject.

Using the USA and EU definitions of rare health conditions (50-64 per 100,000 people per year), in Namibia with a population of about 2 400000 translates to 1000 neural tube defect cases per 100, 000 people per year. This study focused on three regions, namely; Oshana (176 674), Oshikoto (181 973) and Ohangwena (245 446) with a total population of 604 093 (2011 Housing and Population Census, 2011). The expected number of cases is calculated to be at about 600 per 604 093 people per year. Thus, waiting to get a large number of rare cases may take up to 20 years to collect and reach the specified number of rare conditions required. Therefore, Gagne et al. (2014) highlight the fact that the most obvious challenge to conducting research on rare diseases/conditions is the small number of eligible participants expected for the study and lack of appropriate comparators treatments. For this reason, they advocated for a paradigm shift in clinical research methodology on rare health conditions.

5.2. INCIDENCE OF NTDs PER 10000 BIRTHS

The key findings that emerged from the results on the incidence of NTDs at the two hospitals were categorised as per the distribution of cases and type of NTD per hospital, distribution of NTD cases and type per region as well as the overall incidence of NTDs. It was found that the combined incidence of NTDs of 11 per 10000 births may not be clinically overlooked. The incidence of 11 per 10000 births is important because it is well above 8 per 10 000 births reported in the literature as representing the lower limit of a high incidence that requires preventative intervention (Crider et al., 2014).

Subsequently, Gedefaw, Teklu, & Tadesse, (2018) stated that the cut off level could even be reduced to 5 per 10000 births, indicating that the cut off level of 8 per 10000 births may lead to underestimation of the magnitude of the problem. This suggested that incidence of 11 per 10000 births can be an underestimation, since babies with neural tube defects born in hospitals other than Oshakati and Onandjokwe were excluded. During this period, there were no stillbirths recorded. In addition, Oshakati and Onandjokwe hospitals did not carry out an early termination of pregnancies affected by neural tube defects. Oshikoto region was found to have the highest number of cases of babies with NTDs (47%) in comparison to Oshana (33%) and Ohangwena (20%) respectively. These differences can be explained by regional population density and distribution, the proximity to health facilities and the availability of health services in each region.

Onandjokwe Hospital was the largest hospital in the region and the population distribution was far from the Omuthiya and Tsumeb hospitals. Although, the incidence of 11 per 10000 births could represent the Northern regions, it could not be generalized to the whole country. It was an indication of a public health problem in the regions served by the stated hospitals. This was because the two hospitals were the largest in the Northern regions of Namibia and the lifestyles of the inhabitants were similar. This finding suggested that some form of preventive interventions should be considered in the areas where the mothers came from, namely Oshana, Ohangwena and Oshikoto regions. The current NTDs incidence of 11 per 10000 births was based on deliveries in two adjacent hospitals. It reflected the situation in the regions served by the two hospitals. Other regions may be affected differently by NTDs.

A more comprehensive study is suggested to provide information on NTDs in other regions. In terms of the type of NTDs per hospital, hydranencephaly was found to be higher at each hospital than spina bifida. The reason for this difference was not clearly established in this study. Unlike hydranencephaly and open NTDs, which can be detected by clinical examination, mild cases of neural tube defects such as spina bifida occulta might have been missed in the study because of the difficulty of diagnosing them clinically. This could also contribute to the possible underestimation of the incidence. A study on Malawian children over five years, (Adeloye, 2000) also found fifteen cases of hydranencephaly between 1992 and 1997, emphasising the existence of the problem beyond Namibia.

Importantly, this study also found that hydranencephaly, as a cranial NTD variant, was usually not well recognised by many health workers. This was evident from different cases of NTDs reported in the Namibian newspapers at different hospitals in Namibia (“Miracle baby still fighting on - The Namibian,” 2019), (Kooper, 2017) & (Kahiurika, 2019). Often, babies born with ‘big heads’ were initially documented by health workers as having hydrocephalus, which is not a type of NTDs. It could be emphasised here that, with the identified high incidence of NTD (11 per 10,000 births) and with increased proportion of severe cases of hydranencephaly, the estimated costs of treatment would be high.

Sayed et al. (2008) supported the above finding that the benefit of neural tube defects prevention (fortification and supplementation) is greater than the cost of treatment. In the context of South Africa, where fortification is mandatory, the average treatment cost of NTDs was R100, 000.00 per case during the first three years (Sayed et al., 2008). This could translate into savings of R40, 6 million per annum, if 406 NTDs cases were prevented. Using Sayed et al. (2008) estimation, Namibia through the MoHSS could spend N\$100, 000.00 times 15 cases totaling N\$ 1, 5 million per annum. Furthermore, Sayed et al. (2008) reported cost benefit ratios achieved in different countries as presented in the table 13.

Table 13: Cost benefit ratios achieved in different countries

Country	Ratio	Authors & Year
South Africa	30:1	Sayed et al., (2008)
USA	40:1	Grosse et al. (2005) cited in Sayed et al. (2008)
Chile	10:1	Llanos et al. (2006) cited in Sayed et al. (2008)

The above table affirms the benefit of NTDs prevention through mandatory folic acid fortification of food products and supplementation.

In addition, although this study found a higher proportion of severe cases of hydranencephaly than spina bifida, different local media reports did not differentiate between hydrocephalus and hydranencephaly (Koooper, 2017) & (Kahirua, 2019). Since in both hydranencephaly and hydrocephalus, there was usually head enlargement, there were difficulties in differentiating the two conditions. According to a study by Adeloje, (2000) in Malawi, there was a clear distinction between hydranencephaly and hydrocephalus; especially on ultrasound or CT scan of the brain, the two conditions could be differentiated. In hydranencephaly, there was a big head, but the forebrain was not developed and cerebrospinal fluid (CSF) filled the cranial cavity, not ventricles. In other words, cerebral ventricles could not be identified anatomically. The children tend to die early. On the other hand, with hydrocephalus, there was a big head, with brain and ventricles well developed, yet there was a block in circulation of CSF, leading to dilation of ventricles and thinning of cerebral white and grey matter.

As a result, Adeloje, (2000) cautioned health workers to recognise the difference between hydranencephaly and hydrocephalus, to offer appropriate management options and counselling. Since this study focused on environmental factors, another study is required to look at others factors to expand the scope. Obeidat & Amarin, (2010) reported spina bifida as being the most common type of neural tube defects. In Cameroon, Njamnshi et al. (2008) reported 71% spina bifida and only 5.4% anencephaly. In South Africa, Venter, Christianson, Hutamo, Makhura, & Gericke, (1995) reported anencephaly as being more common than spina bifida. The cause of this difference was not established.

In addition, the majority of cases (60%) were delivered at Onandjokwe hospital rather than Oshakati. The high number of cases at Onandjokwe could be because some of the babies from Ohangwena Region were also born there, although babies born in other hospitals like Engela and Eenhana were not captured. Similarly, babies from Omusati Region and Kunene Regions born in Oshikuku, Okahao, Outapi, Tsandi and Opuwo hospitals were not included. Such babies were part of the exclusion criteria in this study. It was also important to state that although stillbirths were not part of the inclusion criteria, there were no stillbirths with NTDs identified during the study. The study further found no significant difference between the mean age of mothers of cases and controls. Maternal age was not associated with any specific type of NTDs in this study. This finding was supported by Teckie, Krause, & Kromberg, (2013) who stated that the association between maternal age and NTDs were not fixed, but variable. This was because babies with NTDs could be borne by any woman at any age, which indicated that age alone had no influence.

On the other hand, Buccimazza et al. (1994) in South Africa and Vieira & Castillo, (2005) in Chile, reported that babies with NTDs were born mostly by mothers younger than 20 and 19 years or older than 35 and 40 years respectively. However, there was no clear explanation for these findings. In terms of BMI, there were no mothers in the obese category from both cases and controls in this study. Frey & Hauser, (2003) stated that maternal obesity was associated with double the risk for NTDs.

5.3. SEASONAL VARIATION IN BIRTH OF BABIES WITH NTDs

This study documented a clear seasonal variation in the birth of babies with NTDs. Retrospectively 80 per cent of NTD affected babies appeared to have been conceived during the “dry season” when fruits and vegetables were relatively unavailable to many mothers. The finding of this study proposed an association between conception, the birth of babies with NTD and local average rainfall. This means most cases were conceived during the dry season and born during the rainy season, which could suggest the existence of a season related high-risk factor at conception. This observation was important, because it may be linked to seasonal local dietary patterns and food availability. It is of interest that seasonal births of NTD babies was observed on two different occasions in the same hospital.

Even though seasonal variation was also reported in two studies globally, (Obeidat & Amarin, 2010) in Jordan, (De La Vega & Ronald, 2009) in Puerto Rico, the explanation for the variation was not clearly provided. In other words, seasonal variation in NTD births was infrequently documented and explained in the literature, but its observation suggested that environmental factors could be playing a role

rather than genetic factors as reported by (Hwang, Magnus, & Jaakkola, 2013) in Norway. In this study, it was further found that babies with spina bifida were conceived between March 2016 and October 2016, whereas babies with hydranencephaly were conceived between February 2016 and November 2016 in Namibia. The conception of babies with NTDs, spinal and cranial, was mostly during the dry season, indicating that there was no difference in season of the conception of mild and severe NTDs. In other words, seasonal variation at conception contributed to the occurrence of NTDs, but not to the severity of the NTDs.

According to the FAO (2005) study, Namibia has low average rainfall, high levels of poverty, food insecurity, lack of appropriate farming methods and high unemployment rate. Pearl millet (Mahangu) was the main staple crop in North-Central Namibia, supplemented by legumes and vegetables such as melon and local dried-spinach (Angula, Thomas, & Ijambo, 2014). There was little food security because of drought and sometimes floods. This suggested that the availability of fruits and vegetables was seasonal and domestically produced. Angula et al., (2014) further stated that the few green scheme projects aimed at improving food security encountered challenges, since rainfall was highly variable, necessitating irrigation farming. The following are examples of folate-rich fruits and vegetables: green spinach, avocados, bananas and oranges (Zhang et al., 2008). Nonetheless, these food products (avocados, bananas and oranges) are not part of the staple diet in the northern regions.

5.4. MEAN POSTPARTUM MATERNAL RED BLOOD CELL FOLATE IN CASES AND CONTROLS

This study found low maternal postpartum red blood folate in both cases and controls, with the exception of two controls, despite the fact that 89% of mothers took folic acid tablets during antenatal care. It was observed that the values/levels were similar in both groups and were mostly very low compared to the preferred periconceptual levels of 906 nmol per litre or more, with the exception of two mothers in the control group. In addition, it was also worth mentioning that there was no significant difference between levels/values in cases and controls.

In other words, the study found no correlation between folate levels and NTD incidence, although all were below the threshold level for NTD in the literature as presented by Crider et al. (2014) of 906 nmol per liter. It was also important and worth mentioning that the average red blood cell folate was lower for hydranencephaly cases (470 nmol per litre) when compared to spina bifida cases (502 nmol per litre), and highest in the control group (611 nmol per litre). This finding indicated the possibility that the lower the value/level of red blood cell folate, the more severe the neural tube defects to be expected. This proposition should be studied on a larger sample.

A study by Ren et al., (2007) conducted in China comparing postpartum red blood cell folate from two areas, one with high NTDs and the other with low prevalence found that the values were 440 nmol per litre and 910 nmol per litre respectively.

In addition, a review article by (Tamura & Picciano, 2006) reported that serum folate declined by 10 nmol per l from 20 to 10 nmol during 40 weeks of pregnancy, which verified a correlation between periconceptional and postpartum folate levels. (Tamura & Picciano, 2006) further presented a correlation between gestational and postpartum folate levels in a table below.

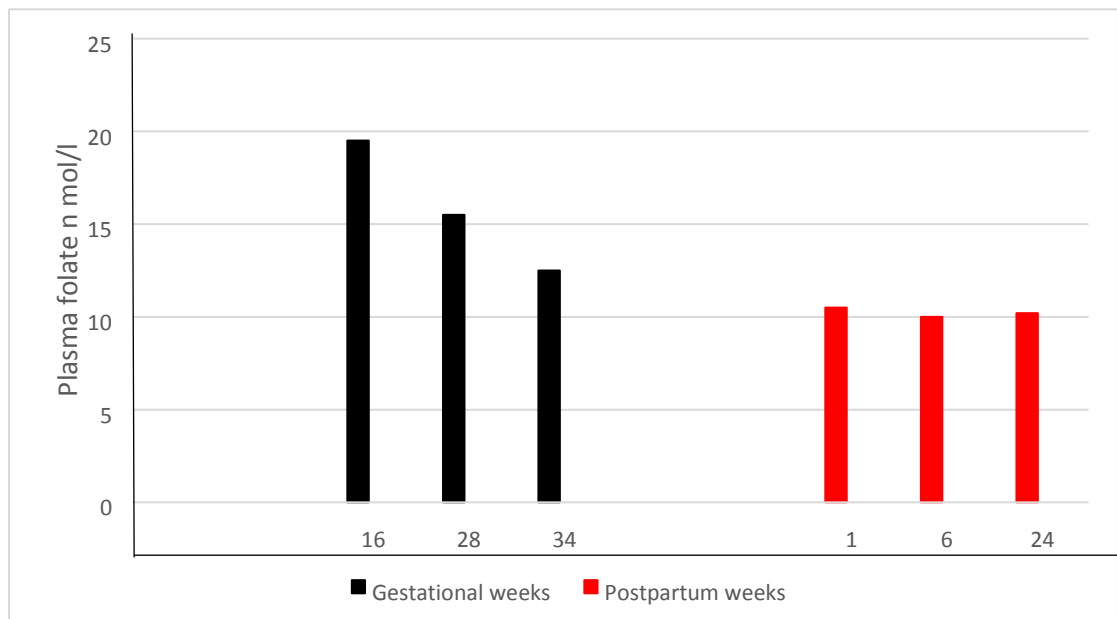


Figure 25. Total Serum Folate in circulation during pregnancy and lactation.

Source: (Tamura & Picciano, 2006)

Figure 25 presents the following: Serum folate declined by 42% between 16 and 34 weeks, Serum folate declined by 10 nmol/l from 20 to 10 nmol/l during 40 weeks of pregnancy and lack of recovery during lactation support suggests that folate nutrition is a continuing burden (Tamura & Picciano, 2006). This indicates that folate level at conception should be expected to decrease up to the time of delivery and to remain low during the breastfeeding period.

As evident in this study, despite the fact that women received folate supplementation during antenatal care, their postpartum folate levels were still low between 196 and 678 nmol per litre. This suggests that periconceptional folate levels were low. It is therefore important to ensure adequate folate levels (equivalent to 906 nmol per litre) periconceptionally. This finding suggested a possibility of low red blood cells folate periconceptionally in the mother population of women in the regions. This could represent a form of maternal malnutrition (Blencowe, Hannah; Cousens, 2010).

It could be concluded that, NTDs were more likely to occur when the periconceptional red blood cell folate was below 906 nmol per litre. According to (Smits & Essed, 2001) maternal red blood cell folate declined from the fifth month of gestation and remained low postpartum. Similarly, (Bates, Fuller, & Prentice, 1986) asserted that without folate supplementation, maternal red blood cell folate dropped to undesirable levels by the third to the sixth month of pregnancy due to increased folate demands.

Clearly, the findings of the above studies affirmed that the postpartum red blood cell folate should be expected to be lower than the periconceptional folate, unless if there was a preventative intervention. This observation suggested that low folate values exist among mothers. In the absence of preventative intervention, there was a high possibility of neural tube defects, intrauterine-growth retardation and miscarriage occurring (Bates et al., 1986). Consequently, it was worth stating that the low postpartum folate in cases and controls signaled the possible existence of low folate in the population, putting babies at risk for development of neural tube defects and other health related conditions.

The findings of this study suggested that there might be a high prevalence of low red blood cell folate in the affected communities such that normal babies born represent a “near miss”. More studies are needed to evaluate the situation.

Furthermore, as from the 1990s, following the findings of the Vitamin study, (1991) periconceptional folate supplementation was recommended to prevent NTDs. This achievement led to the call for periconceptional folate supplementation globally, which resulted in the reduction of NTDs in such countries (Tamura & Picciano, 2006). On the other hand, some researchers and nations expressed concern on the masking of macrocytic anaemia by undiagnosed Vit B12 deficiency when folate acid alone was given. In response, Improved (2017) and Wald et al. (2018) proposed that periconceptional folate supplementation should be combined with Vit B12 for improved impact as was done in Palestine.

In support of the above recommendation, this study concurs with Wald et al. (2018)’s position; withholding the benefit of folate supplementation in preventing NTDs is harmful in itself. In other words, a combination of folate supplementation and Vitamin B12 is recommended to prevent high incidence of NTDs instead of withholding it. Moreover, Improved (2017) established some advantages and challenges in implementing folate supplementation, especially in low and middle-income countries (like Namibia).

Advantages:

- Once implemented, it can be available throughout the year.
- It does not depend on rainfall.
- It is suitable for planned pregnancies.

Challenges:

- It requires government policy and guidelines to be in place.
- It requires allocated public funding.
- It demands a well-informed society for adherence.
- It may not reach all women between 15 – 50 years, especially in rural areas.
- It may not be maximally effective in communities with low educational levels and high-unplanned pregnancies.

The Assembly highly recommended mandatory folic fortification to improve the folate status of women of reproductive age and to decrease neural tube defects and other congenital anomalies. Wald et al. (2018) reported that (by October 2017), 81 countries worldwide carried out mandatory fortification, including 24 countries in Africa and 5 countries in Southern Africa, excluding Namibia. This study therefore recommends mandatory fortification as one of the key strategies in mitigating NTDs, as this approach has the potential to reach every person who consumes the fortified food. It requires national mandatory legislation and partnerships with local industries such as Bokomo, Opoto and Namibmills, and so forth.

Recently, Wald et al. (2018) and Improved (2017) a Micronutrient Forum report recommended that folate and Vitamin B12 fortification should be combined to ensure that macrocytic anaemia and neuropathies are always treated whenever present. In addition, Wald et al. (2018) and Improved (2017) identified advantages and challenges in implementing NTD mitigation interventions and highlighted the need for contextual adaptation of strategies for folate fortification.

Advantages:

- It can be readily available to all citizens.
- It can increase the red blood cell folate in a sustainable way.

Challenges:

- It is not high on the political agenda and is seen as a personal choice by some.
- It requires policies and legal regulations on the type of food and amount of folate needed.
- The majority of the households in some areas of low and middle-income countries (including Northern regions) do not consume commercialised food, but depend on domestically grown and processed foods.
- Not everyone may consume it.
- Unemployed people may not afford fortified food unless it is heavily subsidised.
- Implementation may be time-consuming and expensive.

Therefore, in the context of Northern Namibia with limited rainfall, this study proposed gardening as an additional strategy to maximise availability of folate-rich vegetables and fruits throughout the year. In China, Li et al. (2013) examined geographic and urban-rural disparities and reported that NTD incidence was higher in the North compared to the South due to high consumption of green vegetables in the South.

Furthermore, Shohag et al. (2012) presented folate content and composition of vegetables and fruits as follows: leafy vegetables and 'pak choi' spinach had more than 140µg/100g, whereas roots and fruit vegetables fell below 86µg/100g. Drawing from the above finding, domestic production of leafy vegetables is likely to improve the folate status of the family, especially women of reproductive age. Therefore, considering the seasonal rainfall and availability of vegetables in Northern Namibia, promoting community gardening may increase regular consumption of folate-rich vegetables. Household gardening contributes to self-employment, where formal employment opportunities are limited.

There are advantages and challenges associated with the establishment of community gardening in Northern Namibia.

Advantages:

- Can be established at household or community level;
- Provides a regular source of folate;
- Does not require high-level technical and legal expertise;
- Offers self-employment opportunities for the majority of women and the youth.

Challenges:

- Requires reliable water source throughout the year;
- Requires fencing, shading, manure, piping and gardening equipment;
- Requires water tanks and generators to pump the water.

For the four strategies to achieve the required maximum results there is a need to create additional measures, namely; to develop hospital birth defects registers and to monitor and evaluate the intervention. In terms of birth registers, the hospitals will enter all birth defects (NTDs) as a baseline to determine the impact of education, food supplementation, food fortification and gardening. The birth defects register at the Northern hospitals will feed into a national register of NTDs annually. The strategies will need monitoring and evaluation of the interventions in terms of the following issues:

- Trends in folate status of women of reproductive age and general population;
- Trends in NTDs incidence in the regions;
- Trends in NTD-related health outcomes – emotional impacts, morbidity, mortality and economic impacts;
- Compliance with legal documents and legislations;
- Establishment of partnerships with laboratories – UNAM and Ministry of Health – NIP.

Regarding anaemia among mothers, the study found that maternity ward records revealed that no full blood count results were available to see if macrocytic anaemia was present. However, since 64% of cases and 38% of controls had haemoglobin less than 12%, it could be presumed that folate deficiency considered in this study could be one of the contributing factors. This suggests that there is a need to investigate the cause of anaemia among mothers. The folic acid supplements (tablets) given at antenatal care visits were aimed at the correction of anaemia and to prepare the mother and baby for a safe delivery, rather than the timely prevention of neural tube defects. This study suggested that, it was advisable to focus on primary prevention of neural tube defects starting pre-conceptionally.

Additionally, it might even be more prudent to start preventing folate sensitive neural tube defects soon after menarche, and to continue throughout the reproductive age of women irrespective of whether they were married or unmarried. None of the mothers in the cases and controls in this study was married.

5.5. OTHER RISK FACTORS

In this section, discussions related to other possible risk factors were presented based on the conditions as described in the literature (Salih et al., 2014), mainly social and health related: maternal age, work status, education, diet, alcohol, smoking, marital status, family history, consanguinity, antenatal care, gravidity and parity, diabetes, antiepileptic drugs, exposure to radiation, exposure to extreme temperature, HIV, in addition to red blood cell folate levels, anaemia, and recurrent NTDs.

Work Status

In terms of work status, the study found that 79% of cases were unemployed, while 69% of controls were also unemployed, which demonstrated no difference in the work status of mothers. Since participants in this study were mothers who were unemployed, this finding also proposed a need for a study on incidence of NTDs in mothers delivering in private hospitals, likely to be from a working class. This finding corresponded well with low socio-economic status, which was regarded as a risk factor for NTDs according to (Frey & Hauser, 2003; Salih et al., 2014).

Education

In addition, the level of education of mothers in both groups (cases 60% and controls 69%) was mostly up to secondary school. It was worth mentioning that, there were no significant differences between cases and controls. Frey & Hauser (2003) clearly stated that preventive intervention strategies such as community education on neural tube defects and food fortification were less successful in low socio-economic classes compared to high socio-economic classes.

NTD knowledge

On the knowledge of neural tube defects, the results showed that only 50% of mothers in both groups (cases and controls) in the study had heard of neural tube defects, which was similar and relatively low, indicating the need for promotion of basic knowledge on NTDs. In other words, there was still a need to develop strategies to educate and inform more mothers on this topic in order to assist them in making informed choices regarding prevention options. The proposed intervention strategies were informed by the following documents and studies:

- a) Improved (2017), a Micronutrient Forum document; “Advancing Neural tube defects prevention in low and middle-income countries through improved folate status in women of reproductive age”;
- b) Wald et al. (2018), Public Health Failure in the prevention of neural tube defects: time to abandon the tolerable upper intake level of folate”;
- c) Bailey & Hausman (2018) “Folate status in women of reproductive age as basis of neural tube defect risk assessment”;
- d) Rogers et al. (2018) “Global folate status in women of reproductive age: a systematic review with emphasis on methodological issues”.

Furthermore, the above studies underscored the need to prevent NTDs and to mitigate birth anomalies among children. These scholarly documents by technical experts can serve as useful guide in developing and implementing the proposed strategies and adapting them to local context in the following stages. Different researchers supported education alongside other approaches to prevent NTDs. According to Wald et al. (2018) and Heseke, Mason, Selhub, Rosenberg, & Jacques (2009), public health education programmes on NTDs are complementary and need to be combined with folic acid supplementation and folic acid fortification for them to succeed. This is because none of the approaches will achieve the required maximum preventive results on their own. Furthermore, Heseke et al. (2009) identified the following challenges to be overcome in the fight against NTDs in low and middle-income countries:

- High health illiteracy on NTDs;
- Ineffective communication strategies in terms of language barriers, long distances and limited media access;
- Inadequate support from health practitioners and political leaders.

Apart from the challenges, there are advantages in implementing education and advocacy, such as;

- Promotion of self-motivation and adherence to the use of folic supplementation and fortification by individuals;
- Implementation at minimal cost through primary health care and community leaders.

Gravidity and parity

The gravidity and parity of all mothers were similar and did not suggest an association with NTDs. Stillborn babies with and without NTDs were not found in this study. Furthermore, the two hospitals also did not conduct early termination of pregnancies with NTD babies. Blencowe, Hannah & Cousens., (2010) reported a high incidence of stillbirth in low-income countries in Africa and Asia. Berihu et al. (2019) reported up to 77% of neural tube defects affected babies being stillborn. Therefore, it was important to note that repeated miscarriages and abortion could signal the existence of a risk factor to NTDs.

Diabetes

On the association between diabetes and NTDs, there was only one diabetic mother in both cases and controls, which indicates a risk factor to NTDs. This implied that there is a likelihood of more mothers with diabetes in the population as justified by (Gagne et al., 2014). Likewise, Reece (2012) reported that congenital abnormalities were common in babies born by diabetic mothers. However, the numbers in this study were too small to prove statistical significance by association.

Diet

On the distribution of diet, the study found that 71% of the cases rarely consumed fruits and vegetables, whereas 46% of the controls ate them, which implied that diet low in folic acid could be a risk factor for NTDs. In South China, a diet rich in fruits and vegetables, contributed to low NTD incidence in that region. It can be emphasised that fruits and vegetables are a good source of folate. This implies that

the probability of giving birth to a baby with NTDs among mothers who ate fruits and vegetables was lower than those who did not eat fruits and vegetables.

However, the findings are not statistically significant because the 95% confidence interval included one. This finding was consistent with low socio-economic status in a country where such food was only seasonally available to most people. Those living in the Northern part of Namibia were mostly communal farmers, who lived largely on meals prepared from millet, grown and processed domestically.

Production of fresh fruits and vegetables was not carried out on a large scale at the household level. Naturally, fresh fruits and vegetables were consumed on a small scale during the rainy season, usually after some weeks following the first rainfall. Meat and Fish products were not consistently consumed on a large scale.

Reinforcing the above finding, Melnick & Marazita (1998) reported that the incidence of neural tube defects in Northern China was high compared to Southern China. This was because the consumption of fruits and vegetables was lower in Northern than Southern China.

Alcohol

Regarding, alcohol consumption by mothers, the study found that only 36% of cases, while 31% of the controls consumed alcohol. This means there was no difference in the odds of giving birth to a baby with NTDs among cases and control. In their study, Frey and Hauser (2003) stated that alcohol was not a risk for NTDs.

HIV

On the risk of HIV to NTDs, only 7% of cases tested positive, whilst 15% of controls tested positive, which indicates no difference between the groups. However, this finding is not statistically significant as the 95% confidence interval includes one. It is also worth stating that the two mothers were on treatment. This finding was not surprising because the association between NTDs and folate was established much earlier than the discovery of HIV 1983 (Montagnier, 2010).

In addition, the drugs used to treat HIV in Namibia during the period of this study were not known to cause neural tube defects. However, a recent study conducted in Botswana by (Zash et al., 2019) stated that the use of dolutegravir was associated with NTDs in mothers who took the drug before conception.

Hyperthermia

There was no difference on the odds of giving birth to a baby with neural tube defects among cases and controls as a result of exposure to high temperature. Three out of 13 mothers with neural tube defects affected babies said they were exposed to hyperthermia. The details of the exposure were not clarified. Since the numbers were small, the significance of this finding could not be established, and the proportions were the same in the cases and controls. Frey & Hauser, (2003) indicated that the use of hot tub and sauna in the first trimester of pregnancy could increase the risk of NTDs by up to three times. However, the use of hot tub and sauna was not common in the population studied.

Age

There was no difference observed between the age groups.

Obesity

There was no mother who was categorised as obese in both age groups.

Family history

The study found 7.1% of cases and 7.7% of controls had a positive family history of NTDs. These findings were similar and could be of interest, because they represented a large number of babies in the population, indicating that genetic factors played a role in the observed high incidence found in the two hospitals.

Supporting the above finding, in a letter to the editor, Komolafe et al., cited in (Rocque, Hopson, & Blount, 2018) reported low positive family history in three African countries: Nigeria (0.9%), Uganda (7.8%) and Sudan (1.1%). They attributed the low percentages to the unavailability of available data capturing all cases.

In the state of Alabama, USA, Dupepe et al. (2017) reported that neural tube defect patients had 16.9% prevalence of positive family history, most likely due to genetic factors. This is because the use of folate in that country is already high.

Haemoglobin

Since both cases and controls had patients with anaemia, this could suggest a general nutritional deficiency factor. This study did not investigate the possible causes of anaemia.

Radiation exposure

Only 7% of cases were reported to have been exposed to radiation. The role of exposure to radiation in cases needs further evaluation in another study to quantify the exposure and timing thereof. For the purpose of this study, any relationship between NTD and exposure to radiation cannot be concluded. The numbers were small and the details were not clearly documented. This risk factor could not be fully evaluated in this study.

Antenatal care folate

Nearly all mothers (both cases and controls) who delivered at the two hospitals attended antenatal care, but none of the NTDs were detected during such visits.

Although the antenatal care protocol included demography data, urine examination and ultrasound, it did not specify NTD screening. This finding suggested challenges in early detection of NTDs at the two hospitals. Obeidat & Amarin (2010) stated that this was because by the end of the first month after conception, NTDs were already present. This demonstrated a gap in expertise and tools that focus on early detection of NTDs and related conditions.

Consanguinity and marriage

In addition, it was observed that, none of the mothers had consanguineous relationships and all of them were unmarried. These findings suggest that consanguinity and marriage do not appear to be important contributing factors to NTD.

Drugs

The use of anti-epileptic medications was not found in this study.

Smoking

None of the mothers smoked in both groups. Shafiq (2017) reported that maternal exposure to passive smoking was a risk factor for NTDs babies. Nevertheless, this study did not investigate the role of passive smoking to NTD babies.

5.6. SUMMARY

The results discussed in this chapter were based on small numbers that were not sufficient to prove statistical significance. However, the results were important and robust because of the potential impact they have on the health of the affected population. The study found high incidence of 11 per 10,000 births in Northern Namibia. Seasonal variation was observed in the birth and conception of NTD babies. A link to rainfall was plausible. The related null hypothesis was not rejected. Low postpartum red blood cell folate values were observed in cases and controls with similar mean values, despite folic acid tablets received during antenatal care. The related null hypothesis was not rejected. Many mothers had haemoglobin less than 12 g% (anaemia), which would require further investigation to establish the possible causes. The risk that had plausible contribution to NTDs were identified as; low socio-economic status (unemployment, low level of education), diet low in fruits and vegetables, and low maternal red blood cell folate. Risk factors that had minimal effects were identified as: knowledge of neural tube defects, maternal age, BMI, gravidity and parity, alcohol, smoking, HIV, extreme temperature/hyperthermia, anti-epileptic drugs, radiation exposure, marital status, family history consanguinity. These findings will be used as a guide to develop intervention strategies, recommendations and future research.

CHAPTER SIX: CONCLUSIONS, RECOMMENDATIONS AND INTERVENTIONAL STRATEGIES

6.1. INTRODUCTION

This chapter outlined the conclusions drawn from the study on the high incidence of neural tube defects found in the Northern regions of Namibia. The findings of the study were utilised to make recommendations and develop an interventional strategy for mitigation, early detection and rehabilitation of the established high incidence of neural tube defects (NTDs) in Namibia, starting with the affected Northern regions.

6.2. CONCLUSIONS

Neural tube defects present major health and socio-economic challenges in both global and local contexts, especially in low-resourced countries like Namibia. The study assessed the incidence of neural tube defects in Northern Namibia through a cross-sectional research methodology over 12 months (September 2016 – August 2017) conducted in two referral hospitals. The study found a high incidence of neural tube defects of 11 per 10, 000 births in Northern Namibia. NTDs represent malformations affecting the brain and spinal cord as well as other tissues (Kaufman, 2004; Salih et al., 2014). They cause significant morbidity and mortality. Treatment is often challenging and palliative, with long-term disabilities for the patient and socio-economic strain to both parents and the state. Hydranencephaly was the most prevalent type of NTDs (67%) and spina bifida the rarest at (33%) found in the Northern regions of Namibia.

In addition, the study identified high risk factors, namely; diet (low in fruits and vegetables), low socio-economic status, family history and diabetes. There was a

significant association between conception of babies with NTDs, rainfall (season) and diet. Most NTD-affected babies – cases - (80%) were conceived during the dry season when fruits and vegetables were not available. The high incidence of NTDs was associated with high a conception of NTD-affected babies during the dry season when rainfall was low and the consumption of fruits and vegetables by mothers was low. This is because most mothers were unemployed and relied on rain-dependent fruits and vegetables. The study found low (196 – 678 nmol/l) postpartum red blood cell folate below the optimal peri-conceptual level of 906 nmol/l among mothers, even though folate supplements (tablets) were given during antenatal care visits. This finding suggested the probable existence of prevalent folate insufficiency. The folate insufficiency was likely to be part of wider micronutrient malnutrition in that community.

Notwithstanding the statistically small number of NTD cases (15 cases), the clinical significance was high, thus requiring measures to mitigate the impact. The high incidence of NTDs and micronutrient malnutrition were not only a local concern, but also a national and global priority (Venter et al., 1995; Adeloje, 2000; Hannah Blencowe, Cousens, Modell, & Lawn, 2010; Tamura & Picciano, 2006). The evidence provided by this study should prompt Namibia to implement and intensify global and locally adapted strategies to prevent and mitigate the effects of NTDs.

It is worth mentioning and commending efforts made by Namibia in 1994 for passing an “Amendment of Regulations relating to the Standards of food, drugs and disinfectants”. This regulation was a valuable intervention to ensure salt iodisation after the 1992 survey revealed a high prevalence of iodine deficiency ‘goitre’ in the

Northern regions of Namibia in order to reduce micronutrient deficiency related to iodine (MoHSS, 2001). As a follow up to the above intervention, there seems to be no further regulations related to other micronutrients including folate and vitamin B12, which have a role to play in mitigating NTDs.

Furthermore, the United Nations General Assembly, (2000) adopted the millennium development goals (MGDs), with 8 time-bound targets which all 189 UN Member States agreed to achieve by 2015. Goals 4 and 5 sought to reduce child mortality and to improve maternal health respectively. From MDGs to SDGs, WHO (2015) reported on the sustainable development goals (SDGs) with 17 time-bound targets to be achieved by 2030, of which goal 3 focuses on ensuring healthy lives and promoting wellbeing for all at all ages (Veitch, 2006). As a result, Namibia, like all other member states that are WHO signatories, were expected to initiate strategies to achieve these goals.

In addition, Wald, Morris, & Blakemore (2018) reported that, all signatories were required to implement mandatory food fortification in order to improve the folate status of childbearing mothers to contribute to maternal health and mitigate congenital malformations such as NTDs. However, by 2017, only 81 countries had implemented Mandatory Food Fortification (excluding Namibia) (Wald et al., 2018). Therefore, this study proposed the following recommendations as a way to mitigate neural tube defects in Northern Namibia.

6.3. RECOMMENDATIONS

The study identified different key findings that required action that may offer short and long-term solutions. What follows are some of the recommendations, which could be considered and implemented at different levels; national, local and future research in Namibia.

Implementations

1. To share findings with the Ministry of Health and Social Services (MOHSS), UNAM, community leaders, affected communities and the Health Workforce;
2. To mobilise resources to help establish surveillance laboratories in order to minimise lost specimens and results and to ensure that good quality results are obtained in a timely fashion;
3. To establish a national register and policy for NTD and other congenital anomalies;
4. To promote pre-conceptional balanced nutrition in women of reproductive age and to intensify screening for early detection of NTDs during ANC, by doing alpha fetoprotein tests, foetal ultra-sound and maternal red blood cell folate starting in the first trimester; To introduce the above tests in ANC card;
5. To standardise early and long term management of babies born with NTDs;

Research

1. To assess Namibia's readiness to determine the folate status of the population, especially women of reproductive age such as availability of accredited laboratories, technical experts and partners;
2. To advocate for future research to address the gaps identified by this study, namely:
 - a. To study the incidence of NTD in private hospitals (focusing on working women from better socioeconomic backgrounds);
 - b. To establish a national NTD incidence for Namibia;
 - c. To establish baseline red blood cell folate level in women 15 – 50 years in Namibia;
 - d. To study the relationship between red blood cell folate level and severity of NTDs;
 - e. To study additional risk factors for NTDs, e.g. mycotoxins and genetic factors;
 - f. To study baseline red blood cell folate levels during dry and rainy seasons in same population;
 - g. To study red blood cell folate and other micronutrients in population;
 - h. To study causes of anaemia during pregnancy including folic acid deficiency
 - i. To determine if mycotoxins are present in locally produced, stored and consumed food;
 - j. To determine the red blood cell folate of women experiencing abortions and premature labour, as these conditions are common in clinical practice,
 - k. To measure and document folate content of locally consumed fruits and vegetables.

6.4. INTERVENTION STRATEGIES AND APPROACHES

Intervention strategies were proposed to prevent NTDs, for early detection of NTDs as well as treatment and rehabilitation of affected babies and persons. Such strategies need to include pre-conceptional periods, during pregnancy and after delivery as a step to reduce the high incidence and burden of NTDs as outlined below. This subsection proposed strategies aimed at promoting good health, preventing and mitigating the incidence of neural tube defects in the Northern regions of Namibia; NTD education and advocacy, gardening, folate supplementation and food fortification. It is important to note that the proposed intervention strategies serve as a proposed approach to action, rather than projects that this study intends to carry out. The proposed intervention strategies were informed by the following documents and studies:

- a) Improved (2017), a Micronutrient Forum document; “Advancing NTDs prevention in low and middle-income countries through improved folate status in women of reproductive age”;
- b) Wald et al. (2018), Public Health Failure in the prevention of NTDs: time to abandon the tolerable upper intake level of folate”;
- c) Bailey & Hausman (2018) “Folate status in women of reproductive age as basis of NTD risk assessment”;
- d) Rogers et al. (2018) “Global folate status in women of reproductive age: a systematic review with emphasis on methodological issues”.

Furthermore, the above studies underscored the need to prevent NTDs and to mitigate birth anomalies among children. These scholarly documents by technical experts can serve as useful guide in developing and implementing the proposed strategies and adapting them to local context in the following stages.

Stage 1: NTDs Education and Advocacy

The in-depth understanding of NTDs is required in order to mitigate and prevent NTD cases in any society. In this study, knowledge of NTDs in cases and controls was between 46% - 50%, suggesting a need to embark on widespread education and advocacy campaigns. Different researchers supported education alongside other approaches to prevent NTDs. According to Wald et al., (2018) and Hesecker, Mason, Selhub, Rosenberg, & Jacques, (2009), public health education programmes on NTDs are complementary and need to be combined with folic acid supplementation and folic acid fortification for them to succeed. This is because none of the approaches will achieve the required maximum preventive results on their own. Hesecker et al., (2009) identified the following challenges to be overcome in the fight against NTDs in low and middle-income countries:

- High health illiteracy on NTDs;
- Ineffective communication strategies in terms of language barriers, long distances and limited media access;
- Inadequate support from health practitioners and political leaders.

Apart from the challenges, there are advantages in implementing education and advocacy, namely;

- Promotion of self-motivation and adherence to the use of folic supplementation and fortification by individuals;

- Implementation at minimal cost through primary health care and community leaders.

Stage 2: Folate Supplementation

The folate supplementation approach has proven to be effective in increasing red blood cell folate to desired periconceptual levels (906 nmol/l or more) as described by (Crider et al., 2014). It is worth mentioning that Namibia has implemented prenatal folate supplementation aimed at the correction of macrocytic anaemia based on the research findings dating back to the 1960s (Tamura & Picciano, 2006). However, as from the 1990s, following the findings of the Vitamin, (1991) periconceptual folate supplementation was recommended to prevent NTDs. This achievement led to the call for periconceptual folate supplementation globally, which resulted in the reduction of NTDs in such countries (Tamura & Picciano, 2006).

On the other hand, some researchers and nations expressed concern on the masking of macrocytic anaemia by undiagnosed Vit B12 deficiency when folate acid alone was given. In response, Improved, (2017) and Wald et al., (2018) proposed that periconceptual folate supplementation should be combined with Vit B12 for improved impact as was done in Palestine. In support of the above recommendation, this study concurs with Wald et al., (2018)'s position; withholding the benefit of folate supplementation in preventing NTDs is harmful. A combination of folate supplementation and Vitamin B12 is recommended to prevent high incidence of NTDs instead of withholding it.

Moreover, Improved, (2017) established some advantages and challenges in implementing folate supplementation, especially in low and middle-income countries (like Namibia).

Advantages:

- Once implemented, it can be available throughout the year.
- It does not depend on rainfall.
- It is suitable for planned pregnancies.

Challenges:

- It requires government policy and guidelines to be in place.
- It requires allocated public funding.
- It demands a well-informed society for adherence.
- It may not reach all women between 15 – 50 years, especially in rural areas.
- It may not be maximally effective in communities with low educational levels and high-unplanned pregnancies.

Stage 3: Food Fortification

The World Health Organisation (WHO) (2010) during the 63rd World Health Assembly resolved that member countries should implement primary prevention of birth defects (including NTDS) to contribute to the attainment of (6) Sustainable Development Goals by 2030. The Assembly highly recommended mandatory folic fortification to improve the folate status of women of reproductive age and to decrease neural tube defects and other congenital anomalies.

Wald et al., (2018) reported that, by October 2017, 81 countries worldwide carried out mandatory fortification, including 24 countries in Africa and 5 countries in Southern Africa, excluding Namibia.

This study therefore recommends mandatory fortification as one of the key strategies in mitigating NTDs, as this approach has the potential to reach every person who consumes the fortified food. It requires national mandatory legislation and partnerships with local industries such as Bokomo, Opoto and Namibmills. Recently, Wald et al., (2018) and Improved, (2017) a Micronutrient Forum report recommended that folate and Vitamin B12 fortification should be combined to ensure that macrocytic anaemia and neuropathies are always treated whenever present.

In addition, Wald et al. (2018) and Improved (2017) identified advantages and challenges in implementing NTD mitigation interventions and highlighted the need for contextual adaptation of strategies for folate fortification.

Advantages:

- It can be readily available to all citizens.
- It can increase the red blood cell folate substantially.

Challenges:

- It is not high on the political agenda and is seen as a personal choice by some.
- It requires policies and legal regulations on the type of food and amount of folate needed.

- The majority of the households in some areas of low and middle-income countries (including Northern regions) do not consume commercialised food, but depend on domestically grown and processed foods.
- Not everyone may consume it.
- Unemployed people may not afford fortified food unless it is heavily subsidised.
- The implementation may be time-consuming and expensive.

Therefore, in the context of Northern Namibia with limited rainfall, this study proposed gardening as an additional strategy to maximise availability of folate-rich vegetables and fruits throughout the year.

Stage 4: Gardening

It is recommended that community gardens should be established to produce fruits and green vegetables throughout the year that are rich in folate content for household consumption, with a primary focus on women; e.g. oranges, bananas, avocado, and spinach.

Eating fresh green vegetables, at least once a week reduced NTDs and congenital heart disease whereas potato consumption increased their risk (Zhang et al., 2008). In China, Li et al. (2013) examined geographic and urban-rural disparities and reported that NTD incidence was higher in the North compared to the South due to high the consumption of green vegetables in the South. Furthermore, Shohag et al. (2012) presented folate content and composition of vegetables and fruits as follows: leafy vegetables and ‘pak choi’ spinach had more than 140µg/100g, whereas roots and fruit vegetables fell below 86µg/100g. Drawing from the above findings, domestic production of leafy vegetables is likely to improve the folate status of the family, especially women of reproductive age.

Therefore, considering the seasonal rainfall and availability of vegetables in Northern Namibia, promoting community gardening may increase regular consumption of folate-rich vegetables. Household gardening contributes to not only self-employment, where formal employment opportunities are limited but also to community empowerment towards self-help and sustaining food security.

The advantages and challenges associated with the establishment of community gardening in Northern Namibia can be listed as follow:

Advantages:

- Can be established at household or community level;
- Provides a regular source of folate;
- Does not require high-level technical and legal expertise;
- Offers self-employment opportunities for the majority of women and the youth.

Challenges:

- Requires reliable water source throughout the year;
- Requires fencing, shading, manure, piping and gardening equipment;
- Requires water tanks and generators to pump the water.

For the four strategies to achieve the required maximum results there is a need to create additional measures, namely; to develop hospital birth defects registers and to monitor and evaluate the intervention.

In terms of birth registers, the hospitals will enter all birth defects (NTDs) as a baseline to determine the impact of education, food supplementation, food fortification and gardening. The birth defects register at the Northern hospitals will feed into a national register of NTDs annually.

The strategies will need monitoring and evaluation of the interventions in terms of the following issues:

- Trends in folate status of women of reproductive age and general population;
- Trends in NTDs incidence in the regions;
- Trends in NTD-related health outcomes – emotional impacts, morbidity, mortality and economic impacts;
- Compliance with legal documents and legislations;
- Establishment of partnerships with laboratories – UNAM and Ministry of Health – NIP.

6.5. LIMITATIONS

The study was only carried out in two hospitals in Northern Namibia. This limits the full generalization of findings to the whole country. It focused on state patients only, while private patients were not included in the study. The role of mycotoxins in the diet was not evaluated and some maternity records were found to be incomplete. NTDs were diagnosed based on clinical criteria after delivery. Minor NTDs that were not clinically obvious might have been missed. Only English literature could be reviewed during the study. On the design, the following limitations are being acknowledged; a) narrow Lickert scale used, b) exclusion of ANC records in the Questionnaire and c) missing assessment of Blood Sugar in the questionnaire.

6.6. SUMMARY

This chapter noted the high incidence of NTDs established by the study and the identified relevant risk factors. The existence of pre-conceptional micronutrient deficiency in mothers in the Northern regions was emphasised. Recommendations to be implemented through the MoHSS were proposed and areas for future research were listed. Four (4) interventional strategies were identified together with guiding documents to help formulate locally adapted strategies to prevent NTDs. Advantages and challenges associated with each strategy were pointed out. Henceforth, folic acid and Vitamin B12 should be given together in all preventive efforts. Namibia appears to have lagged in the prevention of NTDs since 1991, when the MRC vitamin study findings were reported. To accelerate progress in NTD prevention, Namibia should strengthen partnerships with stakeholders during planning, implementation, monitoring and evaluation stages of strategies to prevent NTDs.

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APPENDIX

Annexure A: Permission Letter from UNAM

University of Namibia Private Bag 13301 Windhoek, Namibia
PO Box 1406, Kunene Avenue, Windhoek
Tel: 061 291 1111 Fax: 061 291 1112



RESEARCH PERMISSION LETTER

Date: 20/06/2016

TO WHOM IT MAY CONCERN

RE: RESEARCH PERMISSION LETTER

1. This letter serves to inform you that student: **FILEMON AMAAMBO** (Student number: **201512724**, is a registered student in the School of Medicine for the PhD at the University of Namibia. His/har research proposal was reviewed and successfully met the University of Namibia requirements.
2. The purpose of this letter is to kindly notify you that the student has been granted permission to carry out postgraduate studies research. The School of Postgraduate Studies has approved the research to be carried out by the student for purposes of fulfilling the requirements of the degree being pursued.
3. The proposal adheres to ethical principles.

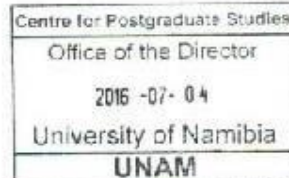
Kind regards,

Signed: *[Signature]* Head PSS for of Health Sc.

Name of Main Supervisor: Prof. S. Hodgson

Signed: *[Signature]*

Dr. M. Hedimbi
Director: School of Postgraduate Studies
Tel: 2063523
E-mail: mhedimbi@unam.na



Annexure B: Ethical Clearance Certificate from UNAM



STUDENT ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: SOM/105/2016

Date: 9 August, 2016

This Ethical Clearance Certificate is issued by the University of Namibia Research Ethics Committee (UREC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the Faculty/Centre/Campus Research & Publications Committee sitting with the Postgraduate Studies Committee.

Title of Project: Assessment of the prevalence and risk factors of neural tube defects including postpartum maternal red blood cell folate in Onandjokwe and Oshakati hospitals.

Nature/Level of Project: Doctorate

Principal Researcher: F. Amaambo

Student Number: 201512724


Host Department & Faculty: School of Medicine

Main Supervisor: Prof. S.V. Hoogson (Main) Prof. C. Hunter; Dr. K. H. Mitonga(Co)

Take note of the following:

- (a) Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the UREC. An application to make amendments may be necessary.
- (b) Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the UREC.
- (c) The Principal Researcher must report issues of ethical compliance to the UREC (through the Chairperson of the Faculty/Centre/Campus Research & Publications Committee) at the end of the Project or as may be requested by UREC.
- (d) The UREC retains the right to:
 - (i) withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,
 - (ii) request for an ethical compliance report at any point during the course of the research.

UREC wishes you the best in your research.


Dr. H. M. Kaponda
Director: Centre for Research and Publications
ON BEHALF OF UREC

Annexure C: Permission Letter from Permanent Secretary, Ministry of Health and Social Services



REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13196
Windhoek
Namibia

Ministerial Building
Harvey Street
Windhoek

Tel: 061 - 203 2125
Fax: 061 - 222558
E-mail: m.simasiku@mhs.gov.na

OFFICE OF THE PERMANENT SECRETARY

Ref: 17/2/3
Enquiries: Mr. M. Simasiku

Date: 31 April 2016

Mr. Filemon Amaambo
P. O. Box 2016
Ondangwa
Namibia

Re: Assessment of the Prevalence and Risk factors of Neural Tube defects including postpartum maternal Red Blood Cell folate in Oandjokwe/ Oshakati hospitals.

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**
 - 3.1 The data to be collected must only be used for academic purposes;
 - 3.2 No other data should be collected other than the data stated in the proposal;
 - 3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;

- 3.4 A quarterly report to be submitted to the Ministry's Research Unit;
- 3.5 Preliminary findings to be submitted upon completion of the study;
- 3.6 Final report to be submitted upon completion of the study;
- 3.7 Separate permission should be sought from the Ministry for the publication of the findings.

Yours sincerely,



Andreas Mwoombola (Dr)
Permanent Secretary

"Health for All"

Annexure D: Request for Permission to Medical Superintendents

P. O. Box 2016

Ondangwa

October 2015

Dr _____

Medical Superintendent

Oshakati/Onandjokwe Hospital

Dear Sir/Madam

RE: Request for permission to conduct Research in

Hospital.

I hereby wish to request permission to conduct research by conducting a quantitative, cross-sectional and case-control observational study in Northern regions of Namibia.

The main purpose is to assess the incidence of neural tube defects per 10000 births in Oshakati/ Onandjokwe hospitals, and to compare postpartum red blood cell folate levels of mothers giving birth to babies with neural tube defects as cases, to the levels of mothers giving birth to normal babies as controls. The possible contributing risk factors will be determined, as well as the possibility of the existence of seasonal variation in the birth of babies with neural tube defects.

A brief summary of the essential details of the research is enclosed for easy reference, particularly its relevance and justification. The research will be conducted through the Faculty of Health Sciences of the University of Namibia (UNAM). Data collection will only start in 2016 after the relevant technical requirements and procedures have been complied with, and continue over a 12 months' period.

Yours sincerely,

F. Amaambo

FRCS.

Annexure E: Request for Permission to the Permanent Secretary, MOHSS

P. O. Box 2016

Ondangwa

October 2015

The Permanent Secretary

Ministry of Health and Social Services

Windhoek

Dear Sir

RE: Request for permission to conduct Research in Oshakati and Onandjokwe Hospitals.

I hereby wish to request permission to conduct research by conducting a quantitative, cross-sectional and case-control observational study in Northern regions of Namibia.

The main purpose is to assess the incidence of neural tube defects per 10000 births in Oshakati/ Onandjokwe hospitals, and to compare postpartum red blood cell folate levels of mothers giving birth to babies with neural tube defects as cases, to the levels of mothers giving birth to normal babies as controls. The possible contributing risk factors will be determined, as well as the possibility of the existence of seasonal variation in the birth of babies with neural tube defects.

A brief summary of the essential details of the research is enclosed for easy reference, particularly its relevance and justification. The research will be conducted through the Faculty of Health Sciences of the University of Namibia (UNAM).

Data collection will only start in 2016 after the relevant technical requirements and procedures have been complied with, and continue over a 12 months' period.

I also wish to seek approval for the Ministry of Health to cover laboratory expenses for the analysis of blood samples for red blood cell folate in cases and controls. This cost is estimated to be below N\$ 15000.

Yours sincerely,

F. Amaambo

FRCS.

Annexure G: Informed Consent – Oshiwambo Version

OSHIWAMBO TRANSLATION

Ngame _____ **ID/Evalo**

_____, otandi gandja ezimino memanguluko, ndi kuthe ombinga momapekapeko guulema wuuluyi novitamine ya folate, sho nda fatululilwa nawa, nonda uvuko, mwa kwatelwa omaupyakadhi nomauwanawa tashi vulika ga holoke. Omaupyakadhi otaga vulu okukala gopalutu, gopamaiyuvo, gopankalo, gopaliko nenge gopaveta. Kapena omauwanawa gu ukilila ndje ihe oshigwana pamwe nongame ohashi vulika shi ka mone uuwanawa komeho shiikwatelela kiizemo.

Ondi uviteko wo kutya onda manguluka okwiikuthamo, pakushanga, uuna nda lundulula omadhiladhilo gandje komeho, nonda manguluka wo okupula omapulo ge na sha nomapekapeko ngaka nokomeho ngele osha pumbiwa. Omafatululo oga gandjwa _mOshiingilisa/mOshiwambo, elaka ndyoka handi uvuko nawa.

Eshaino	Esiku	Ehala
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Omupekapeki	Ongodhi
--------------------	----------------

Ombangi

Annexure H: Information to Participants – English Version

INFORMATION TO PARTICIPANTS IN RESEARCH

1. What is research?

Research is a scientific process to find answers to questions of interest in order to generate new knowledge that can be generalized.

There are many types of research.

2. Why is research needed in health sciences?

Research helps health professionals to understand how the body functions, find out causes of diseases, workout strategies of prevention and treatment.

3. Is participation in research safe?

Participation in research can have potential harm. This is the reason why before research is conducted the planned research has to be checked by experts if it is safe and likely to yield useful information. Harmful research is generally not allowed.

Research can be associated with “discomfort” e.g. pain experienced when blood is taken from a participant. Harm can be physical, emotional, social, economic or legal.

4. **What additional information does a person need before deciding to participate in research?**

- Purpose of research.
- Possible risks to the participant and possible benefits usually to others (society).
- Participation is voluntary, no coercion is used.
- Need to sign informed consent.
- Consent is signed by those legally qualified to sign it or by their legal guardians.
- A participant has a right to withdraw from participation.
- People are generally not paid to induce them to participate, but may sometimes be assisted with basic needs e.g. transport, a meal for the day.
- Research information is treated strictly confidentially.
- The researcher and other relevant committees usually undertake to see to it that the research participants are not harmed by the research or to keep any possible harm minimal.

5. Proposed research

Some babies are born abnormal, with neural tube defects i.e. some malformations of brain and or spinal cord development.

Some babies die early, some undergo expensive treatments to support them to cope with the disabilities.

It is known that lack of vitamin = folic acid, in mother during early pregnancy can result in baby born with a neural tube defect.

The planned research aims at comparing folic acid levels of mothers with neural tube defect babies with that of mothers with normal babies and to document the burden of the problem/prevalence in the studied population. If a significant association is found between neural tube defects and low folic acid, then recommendation will be made to increase serum folic acid in women before future pregnancies occur. There are several options to do this.

This research is needed to hopefully reduce the number of babies born with neural tube defects in future, in the studied population. You need to participate as either a mother with a baby with neural tube defect or a mother with a normal baby for comparison.

The research is called a quantitative, cross-sectional and case-control observational study.

What is required from the participants is for them to understand the potential usefulness of the study, the potential risks involved, if any, and to voluntarily agree to give about 5ml blood to be tested in laboratory for folic acid levels.

The sample shall not be used to test for anything else without their consent.

After the study, the samples will be destroyed.

The researcher will have access to your clinical records in hospital for more information.

The research findings need to be published scientifically.

Annexure I: Information to Participants – Oshiwambo Version

OSHIWAMBO TRANSLATION

Omafatululo kaakuthimbinga momapekapeko

1. **Omapekapeko oshike?**

Omapekapeko ogo omukalo gopaunongononi gokukonga omayamukulo komapulo opo ku monike uunongo uupe tau vulu oku taandelithewa.

Oku na omapekapeko gomaludhi ogendji.

2. **Omolwashike omapekapeko ga pumbiwa muunamiti?**

Oga pumbiwa opo aanawino muundjolowele ya tseye nkene olutu talu longo, nkene omavu haga holoka, nokumona omikalo dhokukeelela nokupanga.

3. **Okukutha ombinga momapekapeko oku na tuu egameno? Okukutha**

ombinga momapekapeko otashi vulika shi ete oshiponga, nomolwaasho manga inaaga ningwa aatseyinawa oyena okudhinda nawa ngele egameno olya gwana tuu, noshizemo sha tegelelwa ngele otashi kwatha tuu shili. Omauwinayi ohaga vulu okukala gopalutu, gopamiyuvo, gopankalo, gopaliko nenge gopaveto.

Omapekapeko ohashi vulika ge ete okauwehame ngaashi pethimbo omuntu ta kuthwa ombinzi.

4. **Iinima yini ya gwedhwa po, omuntu a pumbwa oku yi tseyo manga inaa tokola oku kutha ombinga momapekapeko?**

Yimwe oyo:

- Elalakano lyepekapeko.
- Uuwinayi (ngele ope na) nuuwanawa kaantu yalwe. · Ekuthombinga ihali thiminikile, lyo ihali ningwa nomuheka
- Eshaino lyezimino lyoku kutha ombinga.
- Ezimino oha li shainwa kumboka yena uuthemba wopaveta oku shi ninga, nenge aakalelipo yawo yopaveta.
- Omuntu oha vulu okwiikuthamo momapekapeko, ngele ina hala we.
- Aakuthimbinga ihaa futwa, ihe ohaa vulu okukwathwa ngaashi momalweendo, nenge okupewa sha shokulya.
- Omauyebele gomapekapeko ohaga kwatwa nawa (haga pewa ashike mboka ye ga nuninwa).
- Omupekapeki pamwe nuungundutonateli oye na oshimpwiyu ya gamene aakuthimbinga kaaya ehamekwe komapekapeko, nenge okukaleka omachamo gashonopala ngaashi tashi vulika.

5. **Omapekapeko ga thanekwa Uunona wumwe ohau valwa nuulema wuuluyi nehukamugongo. Wumwe ohau si mbala, na wumwe ohawu ningilwa omatando omanene oku wu kwatha opo wu kale hwepo monkalamwenyo.**

Osha tseyika kutya uuna yina keena ovitamine = *folic acid* ya gwana petameko lyuusimba, okanona ohashi vulika ka valwe nuulema wuuluyi nehukamugongo. Omapekapeko otaga lalakanene oku yelekanitha ovitamine *folic acid* mwaamboka ya vala uunona wa lemana naamboka ya vala uunona wu li nawa, noku tala wo kutya omukundu nguka oguthike peni moshigwana.

Uuna ekwatathano lya monika pokati kuulema novitamine inaayi gwana, nena otaku kuthwa onkatu opo aakulukadhi ya gwedhelwe *ofolic acid* kuyele pethimbo lyomategelelo. Opena omikalo dhoku shi ninga. Omapekapeko ngaka oga pumbiwa opo ando ku keelelwe uulema maanona komeho. Oto kutha ombinga onga omuvali gwokanona ka lemana nenge inaa ka lemana opo ku yelekanithwe koku yelekwe uunene womukundu. Shoka sha pumbiwa euvoko lyuuwanawa womapekapeko, omikundu ngele ope na, nokuzimina oku gandja ombinzi +- 5ml okukonakonamo ovitamine. Itaku konakonwa sha shinwe shi ili omuntu ineeshi zimina.

Konima yomakonakono, ombinzi otayi hanagulwapo.

Omupekapeki ota vulu oku tala momapeko goshipangelo omauyelele ga gwedhwapo.

Oshizemo shepekapeko oshina okushangwa paunongononi.

Annexure J: Instructions for Interviewers

INSTRUCTIONS FOR THE COMPLETION OF THE QUESTIONNAIRE

(Researcher/Research Assistants)

As an outcome of the piloting phase, the following instructions accompanying the questionnaire guidelines were compiled to ensure the interviewers apply the same approach to the interview process for data collection of the study. The instructions took into account the three phases of data collection; before (pre) interview, during (intra) the interview and after (post) the interview. It also considers the interview environment, the participant's emotional needs and the conduct of the interviewer.

1. Before the interview

The interviewer should ensure that:

- Participant is in an environment that is conducive and quiet for a comfortable discussion and interview to ensure privacy and confidentiality.
- The interview process is well explained, understood and informed consent signed.

2. During the interview

The interviewer should:

- Keep participant calm, relaxed and interested.
- Be patient when asking the questions.
- Complete the interview within 1 hour.
- Allow questions for clarity.
- Choose spina bifida for babies with mixed defects.
- Recommend brain ultrasound or CT scan for babies with cranial defects.

3. After the interview

The interviewer should:

- Counsel participant if the participant becomes emotionally unstable – e.g. crying etc.
- Thank participant before she goes away.
- Keep records in a secure place.

Annexure K: Questionnaire Guide

QUESTIONNAIRE – STRICTLY CONFIDENTIAL

SECTION A

1. To be recorded: Hospital number _____
Date of birth _____ Age _____
Village/Town _____ Region _____

SECTION B

2. Are you working? Yes/No
3. What is your highest educational level? Primary secondary more
4. State how often do you eat:
- | | |
|----------------------|--------------|
| porridge/rice/potato | often/rarely |
| Meat/fish | often/rarely |
| Fats/oils | often/rarely |
| Fruits/vegetables | often/rarely |
5. Do you smoke? No/Yes
often/rarely
6. Do you take alcohol? No/ Yes
often/rarely
7. Are you married? No/Yes
8. Is your husband/partner also your close blood relative? No/Yes

SECTION C

7. To be recorded: Height _____ Weight _____
Body mass index? _____
8. To be recorded: Haemoglobin (Hb) _____
9. How many pregnancies did you have? _____
10. How many deliveries did you have? _____
11. Did you have any stillbirths? No/Yes
12. Where you tested for HIV? No/Yes negative/positive
13. Are you diabetic? No/Yes
14. Are you taking medicines for epilepsy/cancer/malaria/kidney infection?
No/Yes
16. Did you attend ante-natal care (ANC) during last pregnancy?
No/Yes

How many times

17. How many months/weeks was the pregnancy, when you started ANC?

18. Did you take folic acid tablets during pregnancy? No/Yes
- Starting gestation

19. Were you given radiotherapy in last 5 years? No/Yes
20. Were you exposed to extreme heat during pregnancy? No/Yes
21. Will you agree to give blood sample for red blood cell folate testing? No/Yes

Delivery date _____ Blood taken _____

SECTION D

22. Have you heard of babies born with neural tube defects? No/Yes

23. Did you have a baby born with neural tube defect(s) in the past? No/Yes

24. Which neural tube defect(s) affects current baby? (Tick)

Anencephaly

Hydranencephaly

Iniencephaly

Encephalocele

Meningoencephalocele

Meningocele

Meningomyelocele

Other

Annexure L: Questionnaire Guide – ANC Record



9-1/0172

Republic of Namibia
Ministry of Health and Social Services
ANTENATAL CARE RECORD

General Information

Name of health facility: _____ Reg. No: _____
 Name of patient: _____ District: _____
 Citizenship: _____ Region: _____
 I.D. Number: _____ Age: _____
 Occupation: _____ Religion: _____
 Marital Status: _____
 Residential Address: _____
 Postal Address: _____
 Tel. No.: W: _____ H: _____ Cell: _____
 Next of kin: _____ Relationship: _____
 Postal Address: _____
 Tel. No.: W: _____ H: _____ Cell: _____
 Date of First Visit: _____

Obstetric History

No	Year	Gestation	Place of Birth	Type of Delivery	Indication	Complications	Weight at Birth	Sex	APF	Born Alive V/N	Duration of Breastfeeding

OBSTETRIC HISTORY

Gravida: _____ Para: _____
 Abortion: _____ LNMP: _____ EDD: _____
 Number of living children: _____
 Children who died: _____ Age: _____ Year: _____ Cause: _____

GYNÆCOLOGICAL HISTORY

Menarche: _____ Duration of menses: _____
 Ectopic Pregnancy: _____ Contraception used: _____
 Hysterotomy: _____
 Myomectomy: _____
 C/S: _____ Yes/No: _____
 Operation on cervix: _____ Yes/No _____ Year: _____
 Fibroids/Tumors / Myoma: _____
 Shiroadkar / McDonalds stitch: _____
 Previous papsmear: _____ Year: _____ Results: _____
 Infertility: _____
 STI: _____

MEDICAL HISTORY

Allergies: _____ Anemia: _____
 Rheumatic Fever: _____ Chronic Hypertension: _____
 Cardiac Disease: _____ Diabetes Mellitus: _____
 Renal Disease: _____ Epilepsy: _____
 Chronic Resp. Disease/TB: _____ Thyroid Disease: _____
 Mental disorders: _____ DVT: _____
 Asthma: _____
 Relevant Treatment: _____

SURGICAL HISTORY

Cardiac: _____ Lung: _____
 Neurosurgery: _____ Breast: _____
 Others: _____

FAMILY HISTORY

Diabetes Mellitus: _____ Tuberculosis: _____
 Hypertension: _____ Multiple pregnancies: _____
 Congenital abnormalities: _____ Genetic disorders: _____
 Mental disorders: _____
 Others: _____

SOCIAL HISTORY

Alcohol: YES/NO Smoking: YES/NO Quantity: _____
 Others: _____

TETANUS TOXOID GIVEN (DATES)

TT1: Date: _____ Signature _____ Follow-up date: _____
 TT2: Date: _____ Signature _____ Follow-up date: _____
 TT3: Date: _____ Signature _____ Follow-up date: _____
 TT4: Date: _____ Signature _____ Follow-up date: _____
 TT5: Date: _____ Signature _____ Follow-up date: _____

SPECIAL INVESTIGATIONS

Hb: _____ RPR: _____
 RH: _____ Antibodies: _____

HIV/AIDS

Counselling Patient: Pre Post: Tested: Refused:
 Result: _____ Help B: _____
 Retest: _____
 Partner: Pre: Post: Couple Counselling:
 Result: _____
 CD4: _____ ARV: _____ Feeding options: _____
 Code: _____ Starting date: _____
 TB: Yes/No: _____ Treatment: Yes/No: _____

GENERAL EXAMINATION

Pallor: _____ Abdominal shape: _____
 Weight: _____ kg Varicose Veins: _____
 Height: _____ cm Urogenital: _____
 Thyroid: _____ Deformities: _____
 Breasts: _____ Oedema: _____

HEALTH EDUCATION

Given On
 Diet: _____ Rest: _____ Hygiene: _____ Clothing: _____
 Minor Ailments: _____ STI/HIV/AIDS: _____
 Breast feeding: _____ Exercise: _____
 Danger signs in pregnancy: _____ Travelling: _____
 Family Planning: _____

CHEMOPROPHYLAXIS

Malaria Prophylaxis: _____ (Yes/No)
 Pregamol given: _____ (Yes/No)
 Others: _____

HIGH RISKS

(YES/NO)
 Risk Factors: 1. _____
 2. _____
 3. _____

RECOMMENDED PLACE OF DELIVERY

1. Hospital: _____
 2. Health Centre: _____
 3. Clinic: _____

PREGNANCY OUTCOME

Date of Delivery: _____
 Time of Delivery: _____ Sex: _____ Apgar: _____
 Place of Delivery: _____ Type of delivery: _____
 If assisted: _____ Indication: _____
 Episiotomy: _____
 Tears: _____ Complications: _____

CONDITION OF MOTHER ON DISCHARGE

BP: _____ Pulse: _____ Temp: _____ HB: _____ Feeding Options: _____
 Lochia: _____ Uterus involution: _____ Breast: _____
 Date of Post Natal care: _____