

CLINICAL EPIDEMIOLOGY OF ATRIOVENTRICULAR SEPTAL DEFECTS
AMONG CHILDREN AT WINDHOEK CENTRAL HOSPITAL, 2015-2020

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ABSTRACT

Congenital Heart Disease (CHD) accounts for nearly one-third of all birth defects globally. It is the leading cause of mortality and morbidity among children in low resource settings. Atrioventricular septal defect (AVSD) accounts for 7.4% of the cardiac malformations. Since establishment of the only paediatric cardiac service in Namibia in 2009, number of children diagnosed with CHD has been on an increase. This study aims to assess the clinical epidemiological burden of AVSDs among children in Namibia.

A retrospective cohort study (2015-2020) was conducted using a data collection tool to extract register data of children aged between 0 and 12 years with AVSD at the Windhoek Central Hospital pediatric cardiology department. Patient's diagnostic criteria included clinical and echocardiographic assessment and when relevant, other cardiac imaging. Bivariate analysis will be used to explore the factors associated with AVSD at the confidence level of 95%. Multiple logistic regression models retained significant risk factors at p-value less than 0.05 to determine significant associations. A total of 91 patients with AVSD were captured in the study. Incidence of AVSD was 0.22 per 1000 children. The male:female ratio was 1:1.3. Trisomy 21 was the most common genetic syndrome found to be associated with AVSD, accounting for 51.6% of all AVSD cases. Only an eighth of the cases received corrective cardiac surgery. Of all the cases, 15.4% AVSD cases were diagnosed with already established irreversible pulmonary hypertension and among these 4.4% demised. There was a significant association between AVSD and prematurity with p-value of 0.029.

In conclusion, the study found a significant association between with AVSD and prematurity. Late referral of patients to cardiology clinics has led to late diagnosis and hindered them from receiving appropriate treatment. The study calls for an intensified public health approach to spread the awareness and advocacy of CHD in Namibia.

Keywords: Congenital Heart Disease, Atrioventricular Septal Heart Defects, Trisomy 21, Windhoek Central Hospital

Table of Contents

ABSTRACT	ii
ACKNOWLEDGEMENT	viii
DEDICATIONS	x
DECLARATION	xi
CHAPTER 1.....	1
1.1 Background of the study	1
1.2 Problem Statement	3
1.3 The Purpose of the Study	4
1.4 Research Question.....	4
1.5 Objectives of the Study	4
1.6 Significance of the Study	5
1.7 Conceptual Definitions.....	5
1.7.1 Clinical Epidemiology	5
1.7.2 Atrioventricular Septal Defect	5
1.7.3 Pulmonary Hypertension.....	6
1.7.4 Windhoek Central Hospital.....	6
1.7.5 Congenital Heart Defect.....	6
1.7.6 Down Syndrome.....	7
1.7.7 Eisenmenger Syndrome	7
1.8 Summary	7
CHAPTER 2.....	8
2. LITERATURE REVIEW.....	8
2.1 Introduction	8
2.2 Overview of Congenital Heart Defects	8
2.3 Overview of Atrioventricular Septal Defects.....	10
2.4 Aetiology of Atrioventricular Heart Defects.....	12
2.5 Epidemiology of AVSD	13
2.6 Embryology and Morphological aspects of AVSD	13
2.8 Pathophysiology of Atrioventricular Septal Defects.....	15
2.7 Diagnosing Atrioventricular Septal Defects	17
2.8 Management of AVSD.....	21
2.8.1 Medical Treatment	21

2.8.2 Surgical Treatment	22
2.9 Differential Diagnosis of AVSD	23
2.10 Prognosis of AVSD	23
2.11 Complications of AVSD	23
2.12 Summary	24
CHAPTER 3.....	25
3. Research Methods	25
3.1 Introduction	25
3.2 Research Design and Methods	25
3.3 Study Setting	26
3.4 Study Population	26
3.4.1 Inclusion Criteria.....	27
3.4.2 Exclusion Criteria.....	27
3.4 Sampling	27
3.5 Research Instruments	28
3.6 Data Collection.....	28
3.7 Data Analysis	29
3.8 Research Ethics	29
3.8.1 Permission	30
3.8.2 Informed Consent.....	30
3.8.3 Principle of Autonomy	30
3.8.4 Principle of Non-Maleficence (do no harm)	30
3.8.5 Principle of Beneficence	31
3.8.6 Principle of Justice	31
3.8.7 Right to Privacy, Anonymity and Confidentiality	31
3.9 Summary	32
CHAPTER 4.....	33
4. Results	33
4.1 Introduction	33
4.2 Congenital Heart Disease	33
4.3 Atrioventricular Septal Defects	35
4.4 Follow up and Mortality.....	39
4.5 Summary	40

CHAPTER 5.....	42
5. Discussion, Conclusions, Recommendations and Limitations	42
5.1 Introduction.....	42
5.2 Discussion of the Findings	42
5.3 Conclusion.....	46
5.4 Study Limitations	47
5.5 Recommendations	48
5.7 Summary	50

LIST OF FIGURES

Figure 1: Windhoek Central Hospital	6
Figure 2: Types of Atrioventricular Septal Defect.....	15
Figure 3:Patients assessed at WCH Paediatric Cardiac Clinic between 2015-2020...34	
Figure 4:Patients assessed at WCH Paediatric Cardiac Clinic between 2015-2020..38	

LIST OF TABLES

Table 1: Characteristics of congenital heart disease patients at Windhoek Central Hospital pediatric cardiology clinic for the period (2015 – 2020).....	34
Table 2 Characteristics of 91 cases with AVSD at WCH paediatric cardiology clinic, from 2015 to 2020	37
Table 3: AVSD Risk Factors in congenital heart disease patients at Windhoek Central Hospital pediatric cardiology clinic for the period (2015 – 2020).....	39
Table 4: AVSD Mortality according to sub-type and presence or absence of any syndrome	40

LIST OF ANNEXURES

Annexure 1: Data Collection Tool for Paediatric Congenital Cardiac Patients (AVSD)	57
Annexure 2: Ethical Clearance Certificate.....	58
Annexure 3: Permission letter to conduct the study from the Ministry of Health and Social Services	59
Annexure 4: Data Collection Permission letter from Windhoek Central Hospital Chief Medical Superintendent.....	60

Abbreviations and Acronyms

ACE	Angiotensin-Converting Enzyme
AV	Atrio-Ventricle
AVSD	Atrioventricular Septal Defect
CDC	Centre for Disease Control and Prevention
CHD	Congenital Heart Disease
DS	Down Syndrome
DSCAM	Down Syndrome Cell Adhesion Molecule
DSCR	Down Syndrome Critical Region
ECG	Electrocardiogram
FELTP	Field Epidemiology and Laboratory Training Program
IPCCC	International Pediatric and Congenital Cardiac Code
LUTH	Lagos University Teaching Hospital
MoHSS	Ministry of Health and Social Services
MRI	Magnetic Resonance Imaging
PH	Pulmonary Hypertension
PVOD	Pulmonary Veno-Occlusive Disease
PVR	Pulmonary Vascular Resistance
T-21	Trisomy 21
UNAM	University of Namibia
UREC	University Ethical Research Committee
USA	United States of America
WCH	Windhoek Central Hospital
WHO	World Health organization

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DEDICATIONS

This study is dedicated to my dear parents; Hilma Shiwomwenyo Nelago Ipinge and Jehonia Colin Ipinge who gave me a solid foundation and full support throughout all my studies. I also dedicate this project to my little sister Chelsi Aguste Ndilimeke Ipinge. May this research study be a source of inspiration for all your academic and future career endeavors.

Finally, I dedicate this study to children born with congenital heart disease in Namibia. It is imperative that congenital heart lesions are picked up early, referred to the cardiac center and managed early because each patient's life matters.

DECLARATION

I, Lahja Ndapewa Omagano Ipinge, declare hereby that this study is a true reflection of my own research, and that this work, or part thereof has not been submitted for a degree in any other institution of higher education.

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CHAPTER 1

1. INTRODUCTION

1.1 Background of the study

Congenital heart disease (CHD) is a problem of the heart's structure and function present at birth, affecting the heart or its adjacent great blood vessels, detected either at the time of birth or detected later in life (Tantchou Tchoumi et al., 2011). Worldwide, CHD are the main heart diseases found in children and constitute one of the major causes of infant mortality and morbidity, predominantly in developing countries (Tankeu et al., 2017). It is a public health issue accounting for nearly one-third of all congenital birth defects and also represents more than 20% of perinatal deaths (Van Der Linde et al., 2011). It is the second leading cause of death in the first year of life after infectious diseases (Troeger et al., 2018).

The current global prevalence is estimated at 8 cases per 1000 live births, representing about 1.35 million newborns each year with CHD (Van Der Linde et al., 2011). However, these figures vary worldwide because of variations in referrals and access to care in population-based studies and referral bias in studies where patients are actively screened with echocardiography. For example, the incidence of congenital heart disease in different studies varies from about 4/1000 to 50/1000 live births and, despite advances in detection and treatment, congenital heart diseases account for 3% of all infant deaths and 46% of deaths from congenital malformations in developed countries such as the USA (J. I. E. Hoffman & Kaplan, 2002). It is estimated that 261 247 children died as a result of CHD in 2017 globally (Zimmerman et al., 2020). Africa is thought to have one of the highest prevalence of heart disease in children, including different types of congenital heart defects with variations in prevalence and patterns both within and different regions and countries due to genetic, environmental and

epigenetic differences, the extent of CHD burden is unknown with very little documented data on it (J. I. Hoffman, 2013) (Tankeu et al., 2017).

Atrioventricular septal defect (AVSD), also referred to as the atrioventricular canal defect is the commonest among congenital heart defect accounting for at least 7.4% of the cardiac malformations (Pugnaroni et al., 2020). Globally, the incidence of AVSD has been estimated from 0.24 to 0.31 in 1000 live births with no significant difference in male and female gender, and it has a strong association with Down's syndrome. Atrioventricular septal defect is a heart defect whereby there is a hole between the left and right chambers of the heart, sometimes with a malformed valve between these chambers. Anatomically, it is classified as complete, partial, or intermediate depending on the malformation. AVSD is associated with extra cardiac defects in about 75% of cases and presents strong genetic association (Pugnaroni et al., 2020). The best-known genetic syndrome associated with AVSD is Down Syndrome in 45 % of the cases and other chromosomal syndromes accounts for 15% (J. I. E. Hoffman & Kaplan, 2002), (Pugnaroni et al., 2020)(J. I. E. Hoffman & Kaplan, 2002). Early onset of congestive heart failure is a common complication of AVSD which may occur in the first 5 years of life. If no intervention is taken, it may result in the establishment of irreversible pulmonary hypertension and contribute heavily to avoidable deaths. Therefore, timely diagnosis and surgical correction is essential in order to alleviate symptoms and correct the defects.

In Africa, the vast majority of CHD, and in particular AVSD are not diagnosed prior to birth, due to the severely limited antenatal screening for CHD. Namibia in particular faces similar constraints. Namibia currently only has one state-funded pediatric cardiac department at Windhoek Central Hospital, a tertiary referral hospital in the capital city of Namibia. This is where pediatric cardiac diagnostic and interventional services are

offered. Other district hospitals and rural communities are accessed using different models of outreach and then referred to Windhoek Central Hospital for correctional surgical interventions and catheterization (F. F. Shidhika et al., 2019).

1.2 Problem Statement

Having accurate data on the epidemiological background of the disease may help understand the burden and inform policies and interventions to manage and control the disease. AVSD is diagnosed by clinical examination and confirmed by an echocardiogram. Commonly, AVSD like many other congenital heart defects, is missed or misdiagnosed especially at district health facilities, leading to late diagnosis with poor prognosis. Early diagnosis is vital to ensure correct medical and surgical management.

Congenital heart disease accounts for nine percent of the neonatal deaths in Namibia (World Health Organization (WHO), 2009). It contributes to approximately 10% of all pediatric admissions in Namibia as compared to the proportion of diarrheal (3%) and acute respiratory infection (3%) (Amakali.Kristofina, 2013). This clearly reflects the gravity of the CHD profile in Namibia, yet there is paucity of published data on the clinical epidemiology and burden of the disease in the country. The lack of data could be attributed to unavailable detection modalities and limited diagnostic techniques among the medical teams. This could mean the previous estimates were an underestimation of the disease burden in the country. In contrast, a declining age at diagnosis of congenital heart diseases like AVSD and at surgery in recent years may be attributed to the arrival of a local pediatric heart specialist in 2018, a pediatric trained cardio-thoracic surgeon in 2019 and as well as the increase in training of local doctors with awareness of congenital heart disease and the possibility of treatment in Namibia (F. F. Shidhika et al., 2019). With these areas improved, the diagnosis and

management of CHDs have drastically improved in Namibia and it is demonstrated by the declining age at diagnosis of CHD which it is consistent with similar findings in South Africa, Egypt and Sudan (Zühlke, Liesl. Mirabel, Mariana. Marijon, 2013).

Based on our clinical observations, AVSD was noted to be one of the common malformations among children treated at the Windhoek Central Hospital's pediatric congenital heart department, and we had observed an increase in number of these cases particularly in children born with Down Syndrome.

To the best of our knowledge, there was no published studies assessing the epidemiological burden and surgical outcomes of AVSD interventions among children in Namibia. It was against this background that this study retrospectively reviewed clinical records to assess the clinical epidemiological burden of children, between the ages of 0 and 12, who were diagnosed and managed for AVSD at the pediatric cardiology department at WCH between 2015 and 2020.

1.3 The Purpose of the Study

The study aimed to assess the clinical epidemiological burden of atrioventricular heart defects among children aged between 0-12 at the pediatric cardiology department at Windhoek Central Hospital, between from 2015-2020.

1.4 Research Question

1. What was the clinical epidemiological burden of atrioventricular heart defects among children aged between 0-12 at the cardiology department at Windhoek Central Hospital, between 2015-2020?

1.5 Objectives of the Study

This study aimed at achieving the following objectives:

1. To determine the incidence of children with AVSD aged between 0 to 12 at WCH between 2015 to 2020,

2. To determine the factors associated with children aged 0 to 12 diagnosed with AVSD at WCH between 2015 and 2020.

1.6 Significance of the Study

The data derived from the study emphasized on the gravity of AVSD profile in the country and the need for congenital heart defects to receive similar attention like other conditions of public health concern such as HIV/AIDS, malaria and malnutrition. It highlighted the need for enhanced diagnostic and surgical measures for AVSD and other congenital heart defects. The data may also be significant to the Ministry of Health and Social Services for resource mobilization, priority setting towards the accurate diagnosis and treatment of congenital heart diseases in the country. This study serves as an immense contributor of additional knowledge on clinical epidemiology of AVSD at Windhoek Central Hospital. The scarcity of published data on the subject in the Namibian context is a pointer of current knowledge gap.

1.7 Conceptual Definitions

1.7.1 Clinical Epidemiology

Clinical epidemiology is the application of quantitative techniques to clinical issues such as diagnosis, treatment and assessment of disease risk and prognosis. The discipline relies profoundly on basic concepts of biostatistics and epidemiology and these are applied in a clinical context to provide an evidence base for clinical care (Olsen et al., 2015).

1.7.2 Atrioventricular Septal Defect

This is a spectrum of disorders, ranging from partial AVSDs, intermediate AVSDs to complete AVSDs as well as AVSD associated with heterotaxy syndrome and also Tetralogy of Fallot. All of these defects comprising the spectrum are characterized by the existence of a common AV junction (Chauhan, 2018a).

1.7.3 Pulmonary Hypertension

Pulmonary hypertension is a common pulmonary vascular disease, which is caused by various causes of increased pulmonary artery pressure.

1.7.4 Windhoek Central Hospital

It is one of the only two tertiary referral state hospital in the country, located in Windhoek, the capital city of Namibia. See image below.



Figure 1: Windhoek Central Hospital

Taken from en.wikipedia.org/wiki/windhoekcentralhospital

1.7.5 Congenital Heart Defect

The word “congenital” means existing at birth. Congenital heart defect, also referred to as congenital heart disease is defined as a gross structural abnormality of either the heart or intra-thoracic great arteries that is actually (or potentially) of functional significance (Aburawi et al., 2015).

1.7.6 Down Syndrome

Also referred to as Trisomy 21, Down syndrome is a genetic disorder caused by the presence of all or a portion of a third chromosome 21. Patients typically present with mild to moderate intellectual disability, growth retardation, and characteristic facial features (Karkera, 2021).

1.7.7 Eisenmenger Syndrome

Eisenmenger syndrome is defined as pulmonary hypertension due to longstanding CHD. The two main features of the CHD that can cause Eisenmenger syndrome are high pressures and high flow (Deng, 2021; Kristine et al., n.d.). As the pulmonary vascular resistance approaches and equals the systemic arterial resistance, the left-to-right shunting decreases and is reversed to become right-to-left shunt. The right-to-left shunting results in a higher amount of desaturated blood to the systemic circulation, and the patient becomes visible cyanotic.

1.8 Summary

This chapter covered the general overview of congenital heart disease, AVSD in particular, and the global distribution of disease. The section also covered the global, regional and national prevalence of congenital heart disease. The increase in children born with AVSD presenting at Windhoek Central Hospital was emphasized in the problem statement. The research objectives were also discussed in this chapter. The significance of the study was also discussed in this chapter. Lastly, conceptual definitions used in this study were explained.

The next chapter will tackle literature review of congenital heart disease in general and overview of atrioventricular septal defects in details.

CHAPTER 2

2. LITERATURE REVIEW

2.1 Introduction

Literature review is an analysis of past relevant literature to create a strong foundation and advanced knowledge. It is essential in identifying what has been written on a subject, determining the extent to which a specific research area reveals any interpretable trends or patterns, aggregating empirical findings related to a research question to support evidence-based practice, generating new frameworks and theories and identifying topics or questions requiring more investigations (Paré et al., 2015).

This chapter is dedicated to avail literature on the overview of congenital heart defects and in particular literature on atrioventricular heart defects. The etiology, epidemiology, embryology, morphological aspects of AVSDs as well as its pathophysiology. The clinical diagnosis of AVSD, its management, complications, and clinical significance of atrioventricular septal defects are also discussed in detail. The chapter intends to further dissect the available data on this topic based on the literature review of similar studies carried out previously by other researchers. It relates the current study to the broader on-going correspondence in literature while providing a framework that settles the validity, necessity of the study and setting the benchmark for comparison with the current study.

2.2 Overview of Congenital Heart Defects

Congenital heart disease or congenital heart defect (CHD) is a problem of the heart's structure and function present at birth, affecting the heart or adjacent great blood vessels, detected either at the time of birth or detected later in life. Worldwide, CHD are the main heart diseases found in children and constitute one of the major causes of infant mortality, particularly in developing countries (Tantchou Tchoumi et al., 2011).

Moreover, the prevalence, incidence and mortality of CHD are substantially heterogeneous across the world. The highest reported total CHD birth prevalence was found in Asia (9.3 per 1,000 live births [95% CI: 8.9 to 9.7]), compared with all other continents (all, $p < 0.001$). Europe had the second highest reported total CHD birth prevalence (8.2 per 1,000 live births [95% CI: 8.1 to 8.3]). Africa reported the lowest total CHD birth prevalence (1.9 per 1,000 live births [95% CI: 1.1 to 3.5]). These significant differences between World Bank income groups found high-income countries with the highest reported total CHD birth prevalence (8.0 per 1,000 live births [95% CI: 7.9 to 8.1]; all, $p < 0.001$); upper-middle income countries reported total CHD birth prevalence of 7.3 per 1,000 live births (95% CI: 6.9 to 7.7) and 6.9 per 1,000 live births (95% CI: 6.1 to 7.7) was reported in lower-middle-income countries ($p = 0.013$). No data from low-income countries were available. The incidence of CHD in different studies varied from about 4/1000 to 50/1000 live births globally (Liu et al., 2019). These abnormalities could be life-threatening in early childhood, and children born with severe forms are at 12 times higher risk of mortality in the first year of life (Tankeu et al., 2017). Consequently, hundreds of thousands of children die each year from CHD, while millions more remain in desperate need of treatment in the developing world. These significant geographical differences were reported to be due to limited access to health care, specifically specialized care in many parts of the world. Other observed differences were of genetic, environmental, socioeconomic or ethnic origin, hence the need for further investigation to tailor the management of this global health problem (Van Der Linde et al., 2011).

In Africa, the management of CHD is limited due to an inadequate socioeconomic environment coupled with deficiencies in cardiology, specialized healthcare facilities and human resources. Understanding the epidemiology of CHD incidence along with

mortality is of great interest and of great importance for epidemiologists and policymakers in order to know the disease burden of CHD. Therefore, it is essential to provide evidence-based data that is recent and reliable in order to help estimate the prevalence and incidence of CHD in Africa and to highlight the burden of these abnormalities. It is also vital for the enforcement of effective preventive strategies based on systematic screening of cardiac abnormalities in the perinatal period.

2.3 Overview of Atrioventricular Septal Defects

An atrioventricular septal defect is a common congenital heart defect that is characterized by a variable degree of the atrial and ventricular septal defect along with a common or partially separate atrioventricular orifice (Jacobs et al., 2000). AVSD is also known as the atrioventricular canal defect, and previously it was called an endocardial cushion defect (Boening et al., 2002). It represents 7.4% of all congenital heart malformations. It is a spectrum of disorders, ranging from partial AVSDs and intermediate AVSDs to complete AVSDs. All of these defects comprising the spectrum are characterized by the existence of a common AV junction (Jacobs et al., 2000).

A partial atrioventricular septal defect is characterized by an ostium primum atrial septal defect, separate atrioventricular valves with a common junction, an inlet ventricular septal defect, and a cleft mitral valve. At the same time, the complete form of the atrioventricular septal defect (AVSD) is characterized by a common atrioventricular valve with ostium primum atrial septal defect and an unrestricted ventricular septal defect of inlet type (Calabrò & Limongelli, 2006).

Operations for atrioventricular septal defects carry substantial risks, and these are one of the most challenging groups of children for cardiac surgeons and anaesthetists to take care of. Children with AVSDs, especially the complete AVSD, have a significant

morbidity and mortality (Chauhan, 2018b). The first successful surgical repair of a complete AVSD was done by Lillehei et al. in 1955. Ginde et al. operated on 198 children with complete AVSD between 1974 and 2000. Their overall perioperative mortality was 10.1% with a significant decrease to 2.9% in the late surgical era 1991–2000. The estimated overall survival for the entire cohort was 85% at 10 years, 82% at 20 years and 71% at 30 years (Ginde et al., 2015). However, long-term results from earlier studies (Crawford & Stroud, 2001; Hoohenkerk et al., 2010a) had demonstrated a 15 years survival of 86%–89%. Moreover, despite improved survival, several single-center studies have reported that up to 10% of patients after complete AVSD repair would require a reoperation within 10–15 years (Hoohenkerk et al., 2010a). The improvements in mortality rates in later years was attributed to improvement in perioperative management including techniques of cardiopulmonary bypass (CPB), myocardial protection, anesthetic and postoperative management. Pulmonary hypertension may have contributed to the risk for late mortality; children repaired in the early era were older at the time of surgery and more likely to have pulmonary vascular occlusive disease (Chauhan, 2018b).

A study done at a pediatric hospital in Yaounde, Cameroon, from 2006 to 2014 in 1 666 children with heart disease found 1,230 (73.8%) patients with CHD. Of these, 66 (4.7%) had atrioventricular septal defects and were predominant in patients with clinical features of Down syndrome (90.9%) (Chelo et al., 2016). This study established that heart diseases, dominated by congenital heart defects, represent an important burden in the child's disease in Cameroon. These conditions are unfortunately under-diagnosed, which is why they are usually discovered late; at the stage of complications. These findings are consistent with a study done at Lagos University Teaching Hospital (LUTH), which is a major tertiary medical care center

in Lagos and one of the largest of its kind in Sub-Saharan Africa, from November 2012 to October 2017 (Ekure et al., 2018). Hence, awareness and antenatal screening of expecting mothers, as far as early screening is concerned, are particularly necessary to reduce the predominance of cardiac sequelae. Much remains to be done in terms of training of medical personnel for the early detection of these diseases that are part of the new challenges of Africa at the time of the epidemiological transition.

2.4 Aetiology of Atrioventricular Heart Defects

In almost all patients, the atrioventricular septal defect is caused by genetic and chromosomal abnormalities; most of the time, it is associated with syndromes (Boening et al., 2002). Various syndromes can be divided into autosomal dominant and autosomal recessive. Down syndrome is the most frequent syndrome, and a study by Korenberg et al. in 1992 identified a one heart defect critical region from 21q22.13 to 21qter, about Down Syndrome Critical Region (DSCR) on the long arm chromosome 21 that is thought to be contributing factor to developing AVSD (Maslen et al., 2006). The Down Syndrome Cell Adhesion Molecule (DSCAM) gene has also been described to be associated with an atrioventricular septal defect and other congenital heart diseases in these patients (Tubman et al., 1991). Noonan syndrome and Holt-Oram syndrome are some of the autosomal dominant where AVSD is well described (Kristine et al., n.d.). It has been estimated that 22% of AVSD without Down syndrome or heterotaxy have a Mendelian genetic syndrome (Craig, 2006).

Gestational diabetes and maternal obesity have also been reported to increase the risk of non-syndromic atrioventricular septal defects (Agopian et al., 2012).

2.5 Epidemiology of AVSD

The incidence of an atrioventricular septal defect in the general population has been reported to be 0.24 to 0.31 per 1000 live births (Craig, 2006). It accounts for 7.4% of all cardiac malformations (Jacobs et al., 2000). Although both male and female genders are affected equally, one of the studies suggests a female-to-male ratio of 1.3 to 1.0, especially in patients with Down syndrome (Santoro et al., 2018). Isolated AVSD, which refers to a defect without other intra-cardiac or extra-cardiac malformations, occurs in only one-fifth of the patients (Craig, 2006). This makes isolated AVSD unique among cardiac malformations because almost 75 % of the AVSD's occur in association with a chromosome defect (Kristine et al., n.d.).

2.6 Embryology and Morphological aspects of AVSD

The comprehension of the complete pathogenesis and genetics of AVSD are not fully understood, but studies over the past few decades have improved the understanding of the heterogeneous mechanism of its causation.

Endocardial cushions are paired (superior and inferior) mesenchymal structures located in the common atrioventricular canal in the early embryonic period, and their growth is of prime importance in the development of atrioventricular septum and atrioventricular valves (Craig, 2006; MF et al., 1999). These endocardial cushions fuse at the end of 4 weeks of development and form two atria and two ventricles. Failure of fusion results in a variable degree of atrioventricular septal defect (Maslen et al., 2006).

The types of AVSDs have been classified according to the International Paediatric and Congenital Cardiac Code (IPCCC), based on the atrioventricular valve morphology and its development. Complete AVSDs include an ostium primum defect with a non-

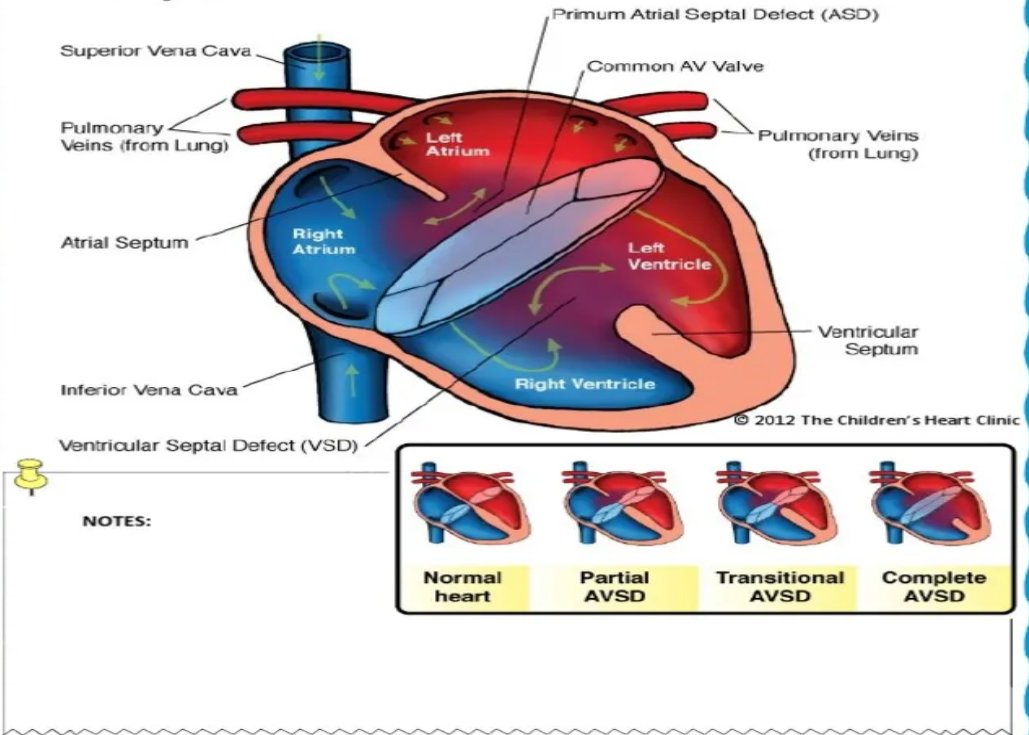
restrictive inlet ventricular defect and a common atrioventricular valve orifice. It is caused by the complete failure of the endocardial cushions to fuse (Pugnaloni et al., 2020). Complete AVSD is characterized by a common AV valve orifice, an interatrial and interventricular communication to a lesser or greater extent.

Partial AVSDs are characterized by separate atrioventricular valves, an ostium primum atrial septal defect, a ventricular septal defect of inlet type, and a cleft mitral valve. It is caused by incomplete fusion of endocardial cushions (Craig, 2006; Pugnaloni et al., 2020). It is the simplest type of AVSD.

Intermediate AVSD, also called transitional AVSD is a term used when a partial AVSD consist of a primum defect in association with a restrictive inlet ventricular defect and two valvular orifices (Craig, 2006).

An unbalanced AVSD is defined as a malalignment of the atrioventricular valve, being unequal for both ventricles. It results in one ventricle receiving more blood flow and the other ventricle being under-developed (hypoplastic) (Crawford & Stroud, 2001; Kristine et al., n.d.).

Atrioventricular Septal Defect (AVSD) Complete



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Figure 2: Types of Atrioventricular Septal Defects

Found on www.scribd.com/document/548508597/atrioventricular-septal-defect-avsd-complete

2.8 Pathophysiology of Atrioventricular Septal Defects

The pathophysiology of AVSD is described essentially in two concepts, namely the hemodynamic components and hemodynamic consequences. The hemodynamic components of interest in AVSD are interatrial shunting, interventricular shunting and AV valve regurgitation. The hemodynamic aspect differs among different subtypes of AVSD as well as with other associated cardiac malformations (Calabrò & Limongelli, 2006; Crawford & Stroud, 2001). There is an increased blood flow through the

pulmonary vascular system as a result of left-to-right shunting through a ventricular septal defect. When the left-to-right shunt is large, the pulmonary arterial pressure and the right ventricular pressure becomes closer to or equal to the systemic pressure. Consequently, pulmonary vascular resistance (PVR) rises rapidly and is elevated after 6-12 months, sometimes much earlier. For this reason, PVR is one of the most significant variables to measure according to timing of surgical repair (Deng, 2021).

The vascular bed in the lungs is a low-pressure system with pulmonary arterial pressure around 12-16 mmHg (Kristine et al., n.d.). Pulmonary arterial hypertension (PAH) is defined by a mean pulmonary artery pressures at rest $>$ or $=$ 25 mm Hg or exercise PA pressures $>$ 30 mmHg. It is a type of malignant pulmonary vascular disease, which is mainly caused by the increase of pulmonary vascular resistance due to the pathological changes of the pulmonary arteriole itself, which eventually leads to right heart failure and death (Deng, 2021; Nishimura & Carabello, 2012).

In respect to different types of AVSDs, there is a difference in developing the increased pressure in the pulmonary vascular bed. In AVSD primum the left to right shunt occurs in a low-pressure system, and for this reason the Pulmonary Veno-Occlusive Disease (PVOD) is developed later in childhood compared to the complete form of AVSD (Mureşan et al., 2016; Nishimura & Carabello, 2012). PVOD is, therefore, a severe hemodynamic consequence of AVSD. It is the correct term used when the vascular disease in the lungs results from a heart defect, which is true in AVSD (Kristine et al., n.d.).

Histopathological changes in the pulmonary vascular bed in PVOD are characterized by vasoconstriction, vascular proliferation and remodelling in the vascular walls. Pulmonary endothelial cells, smooth muscle cells and fibroblast function contribute to

the pathological changes in the vascular bed. In response to increased pulmonary blood flow, the pulmonary vascular bed undergoes remodelling (Deng, 2021; Kristine et al., n.d.). The changes in the vessels lead to an increase in the mean pulmonary artery pressure and pulmonary vascular resistance, and if left untreated, the patient may develop Eisenmenger syndrome (Crawford & Stroud, 2001; Kristine et al., n.d.).

Of interest is that patients with Down syndrome and left-to-right shunt show a more rapid advancement towards PVOD compared to patients without Down syndrome. The reason for the increased risk remains unclear. This calls for further investigations to be performed to uncover the vulnerability that Down syndrome children have to developing PVOD. What is so far known about the Down syndrome population is that they have an underdeveloped midfacial region and upper, making them more prone to recurrent upper airway abnormalities and more prone to recurrent upper airway infection and obstruction. Lung abnormalities such as thinned media of the pulmonary arterioles and a reduction in the number of alveoli (35%) are acquired postnatally due to developmental abnormalities. These factors are considered high-risk factors for pulmonary vascular disease (Aziz et al., 2020; Benhaourech et al., 2016; Santoro et al., 2018).

2.7 Diagnosing Atrioventricular Septal Defects

The diagnosis of AVSD can be made either during pregnancy in the antenatal period by routine obstetric ultrasound or after the baby is born, in the postnatal period. Antenatal diagnosis of AVSD is particularly important because of the strong association with chromosomal problems, especially trisomy 21 (MF et al., 1999). However, antenatal detection of AVSD remain lower than might be expected (Craig, 2006). A study by Ter Heide et al in the United Kingdom found that out of 92

consecutive live born infants with AVSD, only 29% were detected by routine obstetric ultrasound (Ter Heide et al., 2004).

In postnatal period, the diagnosis of AVSD can be made by one or combination of the following. By clinical presentation, electrocardiogram features, chest radiography features, echocardiography and other complimentary imaging such as magnetic resonance imaging (MRI). It's important to note that echocardiographic examination is the cornerstone for the diagnosis of AVSD (Calabrò & Limongelli, 2006).

Pathological findings found on auscultation and clinical examination are generally related to the degree of the left-to-right shunt and presence of left AV valve regurgitation (Kristine et al., n.d.). A patient with AVSD may present with clinical symptoms such as cyanosis, congestive heart failure, right ventricular impulse, accentuated pulmonary component of the second heart sound and / or a precordial murmur. The murmur can vary from being an ejection systolic murmur, an apical mid-systolic murmur (in large left to right shunts) or a pansystolic murmur (with atrioventricular regurgitation) (Crawford & Stroud, 2001).

Patients with partial AVSD habitually present with symptoms of heart failure in the first decade of life, however can be asymptomatic beyond this age. In contrast, the onset of heart failure symptoms in patients with complete AVSD often present earlier, with progressive heart failure usually in the first year of life and in many cases during the first months (St. Louis et al., 2014). The time of onset varies along with the size of the interatrial communication, the interventricular communication and the presence and degree of left AV valve regurgitation (Sassalos et al., 2022). In association with progressive heart failure, tachypnoea, cardiomegaly, failure to thrive, poor peripheral perfusion and increased ventricular activity are some of the characteristics seen in patients with AVSD. If left untreated, nearly all the patients that present with a large

interventricular communication have per definition pulmonary hypertension, and will develop Pulmonary Veno-Occlusive Disease (PVOD) and eventually Eisenmenger complex early in life, and the patient becomes cyanotic (Kristine et al., n.d.).

The chest radiography in AVSD illustrates images that vary along with the degree of shunting and left AV valve regurgitation. There is often enlargement of the right atrium and ventricle, with enlargement of right atrium especially in the presence of left AV (Atrio-Ventricular) valve regurgitation co-existing with the defect. In complete AVSD, cardiomegaly is often more prominent, and can obscure nearly the entire lung fields as a result of a higher degree of left-to-right shunting, and a typical bulge of the upper right atrial shadow together with left and right ventricular dilatation are typical findings on chest x-rays (Chauhan, 2018a; Sassalos et al., 2022). In the presence of heart failure, the chest x-ray may show interstitial pulmonary edema (plethora) and/or areas of pulmonary consolidation and atelectasis due to a possibly secondary compression of smaller airways as a result of abnormally enlarged central pulmonary vessels (Kristine et al., n.d.) Patients who survive the stage of heart failure develop increased pulmonary vascular resistance and when they reach this stage the heart would appear less enlarged on the x-ray, with enlarged central pulmonary arteries and clear lung fields (Kristine et al., n.d.; Sassalos et al., 2022).

The abnormalities of the conduction system in AVSD are the underlying cause of the characteristic electrocardiographical findings. Three main features are described in the literature, PR interval prolongation (first degree heart block), QRS axis deviation and an abnormal ventricular activation (Khairy & Marelli, 2007). The most characteristic feature of AVSD on the ECG is superior orientation of the frontal QRS loop. Other features include prolongation of the QRS complex as well as left and right ventricular hypertrophy (Calabrò & Limongelli, 2006; Kristine et al., n.d.). There also is an

increased risk of complete heart block due to displacement of the atrioventricular node. In patients with AVSD and Down syndrome both the occurrence of non-surgical and late surgical AV block has been observed (Kristine et al., n.d.). Patients with DS could be more prone to this phenomenon because they have a reduced amount of extracardiac mesenchyme at the venous pole which in the end results in that the AV node cannot receive the anterior sino-nodal input (Calabrò & Limongelli, 2006; Sassalos et al., 2022).

Echocardiography is considered the best method for assessing AVSD. Echocardiography, flow imaging, and Doppler interrogation establishes the type of atrioventricular septal defect and assesses the hemodynamic consequences (Khairy & Marelli, 2007; Kristine et al., n.d.). The method is non-invasive, and the diagnosis of AVSD can also be made during fetal life. There are five important morphological goals in echocardiographic assessments of AVSD.

The hallmark in diagnosing AVSD is the absence of the regular crux of the heart and AV valve offset. Echocardiography should assess the relationship between the atrioventricular junction and the underlying ventricles. To establish whether the defect is balanced or unbalanced, ventricular size is important. The fourth goal is the degree of AV valve regurgitation, both the width of the regurgitant jet and the extent of flow into the corresponding atria.

The last morphological feature of importance is the detection of associated cardiac lesions (Khairy & Marelli, 2007; Mureşan et al., 2016). Colour flow imaging and Doppler interrogation are used to establish the levels and degree of shunting between the atria and the ventricles, the competence of the right and left components of the AV valve, and the absence or presence of AV valve regurgitation (Craig, 2006).

Cardiac catheterization is, in most cases, only performed when there is a clinical concern about the possibility of significantly elevated pulmonary vascular resistance (F. Shidhika et al., 2010). This is usually seen in patients with late presentation of AVSD, who are more than six to eight months old. Indications for preoperative cardiac catheterization include evaluation of the pulmonary artery pressure and pulmonary vascular resistance, delineation of branch pulmonary artery anatomy, and assessment of ventricular size for biventricular repair in the situation of unbalanced AVSD. Cardiac catheterization can provide answers about size of the shunting, pulmonary and systemic pressures, resistances and flows. Primary data obtained at cardiac catheterization to measure the degree of shunting includes oxygen content and saturation of the blood in the right atrial, pulmonary arterial, aortic or peripheral arterial blood, and if possible, the left atrial blood (Nishimura & Carabello, 2012).

2.8 Management of AVSD

2.8.1 Medical Treatment

In AVSD, medical treatment is short-term, and it is directed at optimising the patient's condition for corrective surgery (Craig, 2006). It generally includes the use of diuretics, Angiotensin-Converting Enzyme (ACE) inhibitors, betablockers and vasodilators to reduce the preload and afterload to relieve the symptoms associated with pulmonary congestion and heart failure (Chauhan, 2018a; Kristine et al., n.d.). An effectively treated cardiac failure will improve significantly the outcome of the surgery for AVSD. Other associated problems such as feeding difficulties and failure to thrive are managed by tube feeding and providing extra high energy nutritional supplements (Sassalos et al., 2022).

2.8.2 Surgical Treatment

The natural history of AVSD leads to progressive congestive heart failure, late irreversible pulmonary hypertension, and, if left untreated, ultimately death. The ultimate treatment of AVSD is the surgical correction of the defect. Atrioventricular septal repair is a complex surgical procedure and carries operative mortality of more than 3% even in the contemporary era of advanced surgical techniques (St. Louis et al., 2014). Its objectives are to close all septal defects and to repair the atrioventricular valve. Surgical correction of AVSD also carries significant postoperative mortality and morbidity due to residual intra-cardiac shunts, atrioventricular valve regurgitation, left ventricular outflow tract obstruction, and arrhythmias (Chauhan, 2018a). Therefore, an assessment of pre-operative imaging and hemodynamic data is essential for the optimal selection of surgical procedures to reduce the requirement of recurrent surgery and postoperative complications (Hoochenkerk et al., 2010b). In the current era the aim is ideally to provide surgical correction in complete AVSD within the first few months of life and certainly before six months in order to avoid the development of pulmonary vascular disease (Haworth, 1986).

In complete AVSD, surgical closure should be performed in early infancy to reduce the pulmonary vascular disease, whereas, in incomplete atrioventricular septal defect, a repair can be slightly delayed if the patient is not symptomatic. For partial AVSD, the primary repair is preferred with patch closure and atrioventricular valvuloplasty (Craig, 2006).

For balanced complete AVSD, early primary repair with two patch closure techniques is preferred over one patch closure, as one patch closure is associated with an increased rate of recurrent procedures due to patch dehiscence and residual shunt (Crawford & Stroud, 2001). Pulmonary artery banding, which is a palliative surgical procedure is no

longer recommended as a routine procedure in complete AVSD repair unless in the presence of other associated anomalies which make the primary repair a high-risk operation (Vida et al., 2016).

2.9 Differential Diagnosis of AVSD

Common differential diagnoses of AVSD include ostium secundum atrial septal defect, isolated ventricular septal defect and tetralogy of Fallot. The symptoms of heart failure and enlargement of cardiac chambers are common in these malformations, and echocardiogram plays a major role in differentiating AVSD from the aforementioned conditions (Craig, 2006).

2.10 Prognosis of AVSD

The prognosis of untreated atrioventricular septal defect is dismal. Around 50% of the patients die during infancy, either due to heart failure or pulmonary infections (Calabrò & Limongelli, 2006). Those who survive beyond one year develop the irreversible pulmonary vascular disease and later on the reversal of the shunt.

Patients undergoing surgical repair have 15 years of survival of around 90%, and 9% to 10% of those require reoperation within 15 years (Crawford & Stroud, 2001).

2.11 Complications of AVSD

Most of the complications of AVSD are linked to intra-cardiac shunts or atrioventricular valve regurgitation. In complete AVSD, shunting of blood from left to right leads to right-sided overload and signs of heart failure and pulmonary congestion at a very early age, which contributes to significant mortality during infancy. If the shunt is not corrected, it causes an irreversible pulmonary vascular disease that leads to pulmonary hypertension and Eisenmenger syndrome (26).

Regurgitation of blood from the ventricle to atria through the atrioventricular valve leads to pulmonary congestion and enlargement of the atrium. Enlargement of the

atrium can lead to supraventricular arrhythmias. Other complications are related to poor feeding, which may include malnutrition and failure to thrive (Chauhan, 2018b).

2.12 Summary

This chapter covered the overviews of CHD and AVSD. It also covered extensively the etiology, epidemiology, embryology and different morphological aspects AVSD, pathophysiology and diagnosis of AVSD. The medical and surgical treatment of AVSD were also covered in detail, as well as the differential diagnosis, complications and prognosis of the disease.

The next chapter will focus on the research methods.

CHAPTER 3

3. Research Methods

3.1 Introduction

The preceding chapter covered the literature review, which included the overview of CHD and AVSD, the etiology, epidemiology, embryological and morphological aspects of AVSD, pathophysiology, diagnosis, management of AVSDs as well as the differential diagnosis, complications and prognosis of the disease. This chapter discusses research methodology, design and instruments used in collecting data. In addition, the section presents an overview of the study population, sampling, data collection, data analysis and ethical considerations.

3.2 Research Design and Methods

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 (Katzenellenbogen & Hoffman, 2007). Research design is categorized into three forms of inquiry that provide specific guides for actions in a research study, namely: qualitative, quantitative and mixed-method approaches (Creswell, 2014).

A quantitative design is a formal, objective, systematic process for obtaining quantifiable data about the variables of a study. A quantitative approach was applied in this study. To determine the incidence, and identify the factors associated with children diagnosed with AVSD at WCH, a retrospective cohort study of register data was used. The advantages of a cohort retrospective study are that it is less costly and lacks bias because the outcome of current interest was not the original reason for the data to be collected (Mann, 2003).

The choice of study design was determined by the purpose of the study and its objectives. This study aimed to assess the clinical epidemiological burden of atrioventricular heart defects of children at the paediatric cardiology department at Windhoek Central Hospital. The objectives of the study were to determine the incidence of children with AVSD and the factors associated with children aged 0 to 12 diagnosed with AVSD at WCH between 2015 and 2020. The suitable design for this study was a retrospective cohort study design using register data.

3.3 Study Setting

The researcher conducted a retrospective study on the clinical epidemiology of atrioventricular septal defects in children at Windhoek Central Hospital, specifically at the paediatric cardiology clinic.

Windhoek Central Hospital is a tertiary referral hospital in Windhoek, the capital city of Namibia. It is where the only state-run cardiology department/unit is located. The cardiology unit drains patients from all corners of the country and it is a shared department with 4 sub-divisions, namely paediatric cardiology, adult cardiology, cardio-thoracic and cardiac intensive care sub-division. The paediatric cardiology sub-division serves all patients from all over Namibia suspected or diagnosed with congenital heart disease. The register data used for this study belonged to the paediatric cardiology sub-unit and targeted children born with CHD.

3.4 Study Population

The study population in research entails a complete set of people or objects with specified and common characteristics that are of interest to the research (Hulley S & Cummings S, 2007). For this study, the study population was children managed for CHD at the paediatric cardiology department between 2015 and 2020.

3.4.1 Inclusion Criteria

The study included patients aged between 0-12 years with AVSD who were diagnosed, referred, followed up and managed at WCH pediatric cardiology department between the year 2015 and 2020. The diagnosis criteria of patients followed clinical and echocardiographic assessments and when relevant, cardiac catheterization.

3.4.2 Exclusion Criteria

Patients diagnosed with AVSD and had not consulted at the pediatric cardiology unit during the period under review; and patients above 12 years were excluded from the study.

3.4 Sampling

Sampling is a technique of selecting individual members or a subset of the population to make statistical inferences from them and estimate the characteristics of the whole population. This was a retrospective record review study; therefore, the researcher included all participants that met the inclusion criteria for this study. The researcher did not use a specific sampling method but rather extracted data for all children referred and diagnosed with AVSD at Windhoek Central Hospital paediatric cardiology clinic, aged 12 years or below between January 2015 and December 2015. This type of method requires an assessment of a large sample at a limited cost. It therefore minimizes recall bias. Clinical record review also enables easy collection of information which is routinely collected hence it requires less effort and time and it is useful in finding associations (Sarkar S & Seshadri D, 2014). On the hand, some records may have incomplete data or lost in the course of time leading to missing data. The other disadvantage may be the manner in which the information was initially

collected and recorded in the record register might have varied resulting limitation and interpretation of some variables (Sarkar S & Seshadri D, 2014).

3.5 Research Instruments

This study was based on patient's clinical records which contained clinical information recorded in the register book, paediatric cardiology clinic database with pre and post operative data and follow up data. The researcher developed a data extraction form in a Microsoft Excel sheet which was used to extract data from the paediatric cardiology patients register, paediatric cardiology database and follow-up data. The form had sections A to D. Section 1 contained information pertaining to the child socio-demographic background such as date of birth, sex, region, folder number and date of consultation. Section B collected information on the clinical characteristics such as cardiac symptoms observed, cardiac examination results, examination of other systems, presence of co-morbidities, electrocardiogram results. This section also focused on the age when the CHD diagnosis was first made and how the patient was clinically managed. Section C captured the echocardiogram and cardiac catheterization findings of each patient. Section D captured information regarding the outcome of each patient, such as whether the patient received surgical treatment and if yes at what age and the results of the surgery. Whether the patient received interventional catheterization and at the age it was done, and how the patient is doing overall. Or if no intervention was done at all, and if the patient is still alive or has demised.

3.6 Data Collection

Data was extracted from the main register, the paediatric cardiology register at Windhoek Central Hospital cardiac clinic, and it was entered into the developed data collection tool that was detailed in the previous sub-heading. The data collection

process started after an approval letter and an ethical clearance certificate were obtained from the Ministry of Health and Social Services and the University of Namibia Ethical Research Committee (UREC), respectively, as well as from the Windhoek Central Hospital Chief Medical Superintendent. Main researcher collected data between June and October 2022.

3.7 Data Analysis

After the data collection process, the researcher cleaned and analyzed it. Data analysis is the process by which the researcher systematically applies statistical techniques to describe, illustrate and recap the data.

Descriptive analysis in the form of frequencies, proportions and means was used to describe the distribution of socio-demographic characteristics. Data was coded and arranged into variables in the Microsoft Excel sheet. It was then exported into SPSS for the main analysis. The researcher used bivariate analysis to explore the factors associated with AVSD at a confidence level of 95%. The same was used to assess the overall outcomes of patients born with AVSD during the period under review. Significant risk factors at p-value less than 0.05 were used in logistic regression models to determine significant associations.

3.8 Research Ethics

Research studies are expected to adhere to fundamental ethical principles, which are general judgements that serve as a basic justification for human activities and for the protection of participants (Sarkar S & Seshadri D, 2014). The study was carried out by the ethical standards described in the Declaration of Helsinki.

3.8.1 Permission

The University of Namibia Research Ethical Committee (UREC) authorised the study. An ethical clearance certificate was obtained from the University of Namibia Decentralized Ethics Committee. Further approval was obtained from the National Health Research Unit of the Ministry of Health and Social Services (MoHSS) and Windhoek Central Hospital Chief Medical Superintended.

3.8.2 Informed Consent

The study was a record review study with no direct engagement of the participants, and no personally identifiable data was collected, therefore no informed consent was required. Clearance documents detailed in the permission subsection above were obtained before data collection. It is also important to note that it is a departmental policy that an informed consent for “academic and all use of data” is requested from parents / guardians of patients treated at the paediatric cardiology clinic at Windhoek Central Hospital. This consent is taken the first time a patient presents to the paediatric cardiology clinic. Therefore, although this study did not require informed consent from the patients/guardian, it must be noted that a consent for academic and all use of data was signed before at their initial consultation at paediatric cardiology clinic.

3.8.3 Principle of Autonomy

Autonomy refers to the right of an individual to determine what activities they will or will not participate in (Sarkar S & Seshadri D, 2014). This principle was waived since it was a record review study, and permission was granted as fully described in the subsection titled authorization above.

3.8.4 Principle of Non-Maleficence (not harm)

This principle implies that the study should first not harm the study’s participants (Sarkar S & Seshadri D, 2014). The good that was to be derived from the research was

weighed against any potential harm which the study could occasion. Thus, the participants' dignity was respected throughout the study and the researcher had no intention to harm any of the study participants.

3.8.5 Principle of Beneficence

This principle promotes the wellbeing of patients and society (Kong et al., 2008). The study served as a benchmark for the identification of factors associated with patients diagnosed with AVSDs at WCH.

3.8.6 Principle of Justice

This principle deals with fairness and impartiality (Sarkar S & Seshadri D, 2014). All patients from different social, geographical and cultural backgrounds who consulted, followed up and were referred to the Windhoek Central Hospital paediatric cardiology unit with AVSD and aged between 0 to 12 years between 2015 and 2020 were considered equally and formed to be part of the study fairly and impartially.

3.8.7 Right to Privacy, Anonymity and Confidentiality

Regarding right to privacy, anonymity and confidentiality, data was kept confidential and only accessible to the researcher. Medical records were accessed in the department only. No names or any identifiable information, such as names, were collected or published in the study reports. The study included only dependent and independent variables such as demographic profile, primary clinical diagnosis, echocardiography findings, cardiac catheterization, surgery, post-operative morbidity and mortality, and longitudinal follow-up outcomes. Obtained data was treated as anonymous and could not be linked to any personal identifiers. Paper-based data was stored in a restricted lockable cabinet. Data was only used for research purposes and was held in a computer encrypted with a password.

3.9 Summary

This chapter focused on the research design and methods, the population and sample selection used in the study. It also deliberated on data collection and data analysis methods. Ethical consideration for this study was covered. The next chapter is dedicated to the study findings.

CHAPTER 4

4. Results

4.1 Introduction

This chapter is dedicated to data analysis and findings of the study. The study results are based on data collected using the data collection tool as described in chapter three. The results are presented as descriptive and analytical statistics in tables, pie charts and graphs according to the objectives of the study.

4.2 Congenital Heart Disease

Between 2015 and 2020, 708 patients aged between 0 and 12 years suspected to have cardiac disease were referred and seen at Windhoek Central Hospital paediatric cardiac clinic. Cardiac assessment found 419 patients of the total referred patients to have been born with congenital heart disease while 50 patients were assessed with rheumatic heart disease. No structural or functional heart disease was found in 236 patients, who were discharged from the paediatric cardiac clinic. Among the children assessed with CHD, 91 of these children were born with atrioventricular septal heart disease, and these formed the basis of this study.

Figure 1 below presents the final assessment of children referred and seen at the WCH paediatric cardiac clinic between 2015 and 2020.

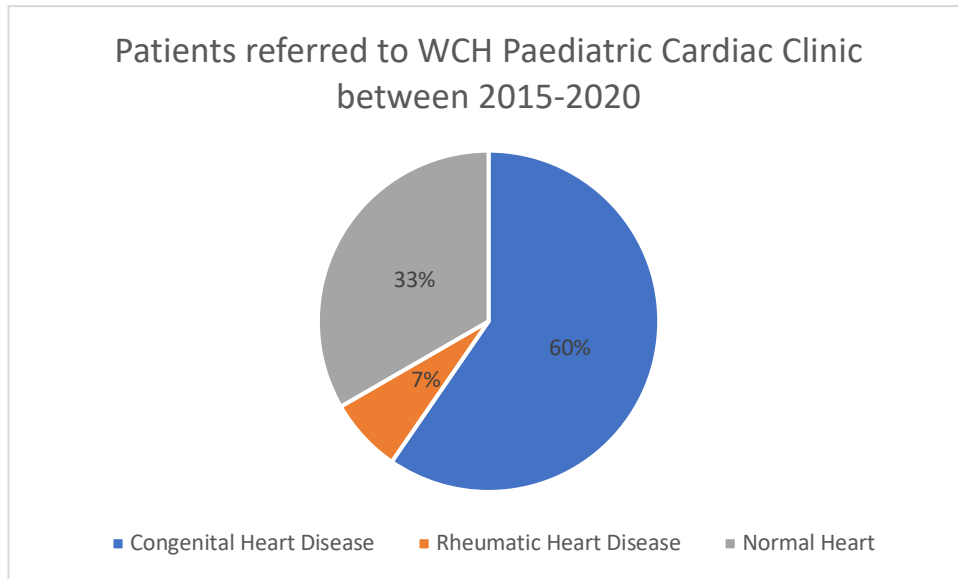


Figure 3: Patients assessed at WCH Paediatric Cardiac Clinic between 2015-2020

The incidence of children assessed with AVSD aged between 0 to 12 at WCH was 0.22 cases per 1000 during the five years.

Table 1: Characteristics of congenital heart disease patients at Windhoek Central Hospital paediatric cardiology clinic for the period (2015 – 2020)

Variable	Category	Outcome		p-value
		AVSD (%)	Others (With no AVSD) (%)	
<u>Sex:</u>	Female	52 (23)	170 (77)	0.369
	Male	39 (20)	158 (80)	
<u>Prematurity:</u>	No	72 (24)	230 (76)	0.057
	Yes	18 (16)	98 (84)	
<u>Syndromic:</u>	No	44 (13)	290 (87)	< 0.001
	Yes	47 (55)	38 (45)	

Table 1 illustrates a summary of the characteristics of the study sample at baseline. Of the 419 children with congenital heart disease, 91 (21.72%) were diagnosed with AVSD. Most children with AVSD were female, 52 (23%), while 39 (20%) were males. The proportion of syndromic patients was found to have a significant risk factor of AVSD among children with congenital heart disease, with a p-value of 0.001. Although the study sample consisted of slightly more females, 222 (53%), than males, 197 (47%), there was no statistically significant difference in the sex orientation between children born with AVSD and those born with other congenital heart conditions other than AVSD. A lower proportion of the children were born prematurely, 18 (13%).

4.3 Atrioventricular Septal Defects

The study population had ages at presentation ranging between 10 days of life to 5 years with a mean age of ± 16.4 months. Just a quarter (25.3%) of cases were diagnosed with AVSD before or at six weeks of age. Almost half of the cases (49.5%) were diagnosed between 6 weeks and 6 months of age.

There was a male: female ratio of 1:1.3 overall but children with atrioventricular septal defect (AVSD) had a higher proportion of female children (52% female to 39% male). The highest proportion of AVSD cases (20.9%) were referred from health facilities in Khomas region, followed by health facilities from the northern regions (Oshana and Ohangwena region) with 11% respectively as showed in figure 2. Syndromes were identified in 48 cases with AVSD, Down syndrome accounting for 97.9% of the syndromic cases and only 2.08% had Noonan syndrome. There was no available data of AVSD cases diagnosed prenatally.

Table 2 shows the types of AVSD cases observed overall and in children with known syndromes. The commonest type of AVSD seen among the cases during the period

under review was complete AVSD (52.3%), followed by partial AVSD (42.9 %) and then transitional AVSD (9.9%). Among the AVSD cases, 37.4% of them had significant pulmonary hypertensive and 26.4% cases had hypothyroidism. Only an eighth of the 91 cases with AVSD had received cardiac surgery, with majority of the cases (64.3%) operated within the first year of life whom are thriving and doing well. Fourteen AVSD cases (15.4%) were diagnosed very late with development of irreversible pulmonary hypertension, which is a complication due to untreated CHD called Eisenmenger syndrome and severe hypothyroidism. Among these cases who were Eisenmenger and were consequently inoperable, 4.4% demised and 11% received palliative medical and supportive therapy during the period under review.

Table 2: Characteristics of 91 cases with AVSD at WCH paediatric cardiology clinic, from 2015 to 2020

Variable	Number of cases	Percentage (%)
<i>Age at Diagnosis</i>		
≤ 6 weeks	23	25.3
6 weeks ≥ 6 months	45	49.5
6 months ≥ 12 months	3	3.3
1 year ≥ 3 years	6	6.6
> 3 years	4	4.4
Sex		0
Male	39	42.9
Female	52	57.1
Types of AVSD		0
Complete	48	52.7
Partial	39	42.9
Transitional	9	9.9
Syndromes		0
Down Syndrome	47	51.6
Noonan Syndrome	1	1.1
Non syndromic	43	47.3
Surgical Intervention status		0
Operated	14	15.4
Not operated	77	84.6

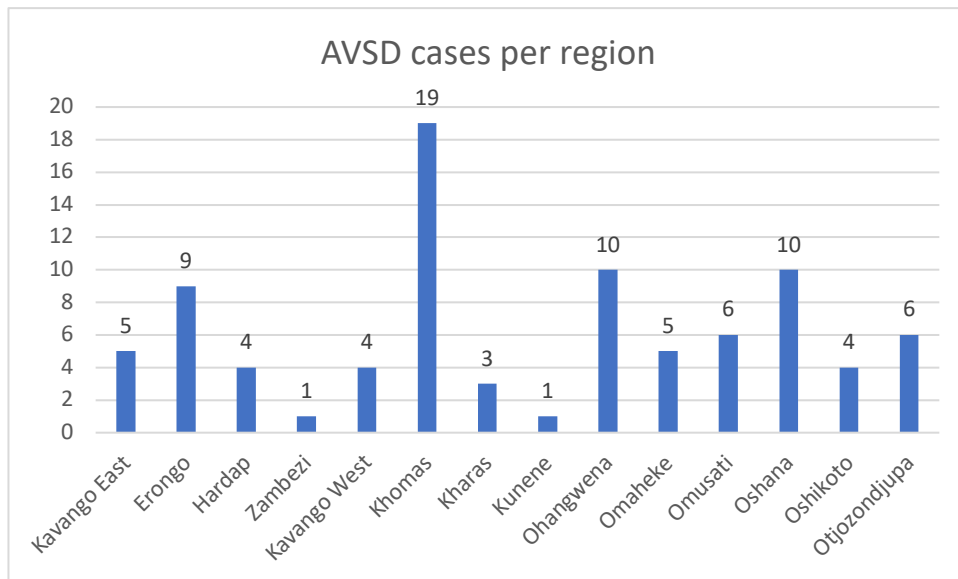


Figure 4: Patients assessed at WCH Paediatric Cardiac Clinic between 2015-2020

Results from the unadjusted and adjusted models are presented in Table 3. The binary logistic model revealed that sex is not a risk factor for AVSD among children with congenital heart disease. However, the model revealed a significantly higher risk of AVSD (AOR = 1.860, 95%: 0.99–3.463) in premature children compared with children born at term. There was a decreased risk of AVSD among congenital heart disease children who were born with trisomy 21, Noonan syndrome or any other syndrome (AOR = 0.120, 95%: 0.070 – 0.206).

Table 3: AVSD Risk Factors in congenital heart disease patients at Windhoek Central Hospital pediatric cardiology clinic for the period (2015 – 2020)

<i>Variable</i>	<i>Crude Odds Ratio (COR)(95% CI)</i>	<i>p-value</i>	<i>Adjusted Odds Ratio (AOR)(95% C.I)</i>	<i>p-value</i>
<u>Sex:</u>				
Male	<i>Ref</i>		<i>Ref</i>	
Female	<i>0.807 (0.505, 1.289)</i>	<i>0.369</i>	<i>0.745 (0.44,1.25)</i>	<i>0.265</i>
<u>Prematurity:</u>				
No	<i>Ref</i>		<i>Ref</i>	
Yes	<i>1.728 (0.980, 3.048)</i>	<i>0.051</i>	<i>1.860 (0.999, 3.463)</i>	<i>0.05</i>
<u>Syndromic:</u>				
No	<i>Ref</i>		<i>Ref</i>	
Yes	<i>0.123 (0.072, 0.209)</i>	<i><0.001</i>	<i>0.120 (0.070, 0.206)</i>	<i><0.001</i>

4.4 Follow up and Mortality

In our study a total of 33 patients, which represent 36.3% demised during follow up period (2015 – 2020). Follow up data was mainly based on data according to those who followed up on their respective follow-up dates given at discharge on previous consultation, the need for medication, and status as alive or demised. Follow up was possible in 89 patients whereas 2 patients were lost to follow up, however upon further investigations, it was later discovered that these 2 cases died at their local health facilities. Of the 33 AVSD patients who demised, 23 (72.7%) were Down Syndrome. Complete AVSD was the subtype recorded with the highest mortality among patients with DS of 70.4 %. Chest infection, heart failure and malnutrition were the major contribution factors to the demise of AVSD cases. Of the 15.4% (14 cases) of the AVSD cases that were operated, 21.4% (3 cases) died in the first 30 days of surgical

correction, and all of them had severe pulmonary hypertension pre-operation which was worsened by severe sepsis in the immediate post-operative period.

Table 4: AVSD Mortality according to sub-type and presence or absence of any syndrome

Diagnosis	Down Syndrome	Non-Down Syndrome	Other Syndrome	Total
Complete AVSD	19	6	2	27
Partial AVSD	4	1	0	5
Transitional AVSD	1	0	0	1

4.5 Summary

This chapter presented data in the form of pie charts, bar graphs and tables. The figures in the graphs, charts and tables were interpreted and discussed in further detail. The key findings derived from this retrospective study can be summarized as follow:

It appears that this is the first study to look into the factors associated with AVSDs at WCH and it established an incidence of was 0.22 AVSD cases per 1000. The study found that the male: female ratio of 1:1.3 in children with AVSD. It also revealed that the age at diagnosis for AVSD differed invariably, between the ages of 0 to 5 years. The study established that complete AVSD was the commonest type of AVSD among children with congenital heart disease at Windhoek Central Hospital. A big proportion of patients diagnosed with AVSD were from healthcare facilities around Khomas region, followed by patients from Oshana and Ohangwena region respectively. The identified risk factors that were associated with AVSD found DS a significant risk factor in children born with AVSD. Although the study sample consisted of slightly

more females, there was no statistically significant difference in the sex orientation between children born with AVSD and those born with other congenital heart conditions other than AVSD. The study also observed that only an eighth of the cases diagnosed with AVSD received cardiac surgery.

In terms of follow up, the study established that majority of patients followed up for their respective consultations at the paediatric cardiac clinic for review and prescription of medication. Less than 5% of the patients did not follow up. From the patients who were operated, none of them required a second operation.

The next chapter is going to discuss study conclusions, which were drawn from the study findings. In addition, the chapter will also look at any challenges or limitations experienced during the study and make recommendations based on study findings.

CHAPTER 5

5. Discussion, Conclusions, Recommendations and Limitations

5.1 Introduction

This chapter will look into the interpretation of the main findings of the study. The findings of the current study will be compared with studies previously done in other countries regional and international literature to bring meaning to the findings. In this chapter, research findings are summarized and concluded in line with the study objectives. Based on the concluding points, recommendations will be generated and limitations of the study will be highlighted in this section.

5.2 Discussion of the Findings

This was the first study conducted at Windhoek Central Hospital to assess the incidence and factors associated with atrioventricular septal heart defects among children born with CHD. It is an important study to set groundwork for further studies.

Of the 419 children aged between 0 and 12 years, born with CHD diagnosed and managed at Windhoek Central Hospital between 2015 and 2020, 91 of them had AVSD. The incidence of children with AVSD at WCH was 0.22 per 1000 live births. This figure is almost similar to the incidence found in the general population which is estimated at 0.24 to 0.31 in 1000 live births (Craig, 2006). The study also found that both genders were approximately equally affected with a male: female ratio of 1:1.3 overall. It is noteworthy that similar pattern was observed in a study done in at the Louis Turcanu Emergency Hospital for Children in Romania, where a male to female ratio of 1:1.2 of children with AVSD(Olariu et al., 2021).

After birth, the age at diagnosis for AVSD differed invariably between day 10 of life and 5 years old with a mean age of ± 16.4 months. This finding of delayed diagnosis

is similar to finding at Gulu Regional Referral Hospital in Uganda where the mean age at diagnosis was 12 months (Aliku et al., 2021).

In this study, the majority of cases diagnosed with AVSD were noted to have been referred from healthcare facilities around Khomas region (20.9%). This is most likely due to the fact that patients did not have to travel long distances to come to Windhoek Central Hospital Cardiac Clinic unlike patients from far away regions who have to wait for hospital transport to be transported to Windhoek and travelling spaces in buses are usually limited to a certain number of patients.

The other factor could be due to the fact that health workers working at facilities in Khomas region have access to ECG machines which help in the diagnosis of congenital heart disease in patients with high clinical suspicion. Big proportion (49.5%) of patients were diagnosed between 6months and 1 year of life, and some diagnosed after the age of 3 years. Late presentation of patients to paediatric cardiology clinic for diagnosis and management is due to several factors. These include misdiagnosis done at primary or secondary health care facilities resulting in late referrals to the paediatric cardiology clinic for proper diagnosis, patients having to travel long distances to get healthcare, insufficient number of skilled health workers in the field of pediatric cardiology. These findings are similar to a study conducted at Lagos University Teaching Hospital, one of the biggest medical centers in Nigeria which is acts as a referral center for paediatric cardiology cases in Lagos, Nigeria (Ekure et al., 2018). That study found that late presentation of cases born with congenital heart diseases, including AVSD at their center was due to inadequate diagnostic equipment and insufficient number of skilled personnel in the field of paediatric cardiology. Having only one paediatric cardiology clinic that is attending to the entire population is also a contributing factor, as the clinic is often fully booked

and booking dates for new patients could be far. Other contributing limiting factors include lack of non-sophisticated equipment such as electrocardiogram (ECG) machines at majority of local hospitals and clinics which can be used to clinically suspect AVSD (Calabrò & Limongelli, 2006).

The bivariate analysis found that there was a strong association between AVSD and prematurity (p-value=0.029). This finding is consistent to a study by Lass et al. (Lass et al., 2012) which reported that prematurity was higher among infants born with AVSD, with a twofold higher.

Cases of AVSD often presented between the age of 0 and 3 years and majority of these were from Khomas region. This could be explained by the fact that patients from clinics, health centers and maternity wards in and around Windhoek are referred early for diagnosis and management. Another reason could be that patients in Khomas region do not have to travel long distances to go to the cardiac clinic unlike patients from other far away regions who have to wait for hospital transport to be transported to Windhoek and travelling spaces in buses are usually limited to a certain number of patients.

Early recognition of lesions is pivotal to obtain the best possible outcome, and education is still needed. It is therefore evident that primary healthcare providers need to have increased awareness of signs related to congenital heart disease, and in particular AVSD.

Trisomy 21 was the commonest clinical phenotypic syndrome found to be associated with AVSD in this study (57%). This is not a peculiar finding as a similar study by Aliku et al in Uganda reported that 80% of AVSD had Down's syndrome (Aliku et al., 2021). While the observation of high number of AVSD cases in Down's syndrome

babies in this study is not surprising, this could be explained by a possible selection bias as Down syndrome babies are usually referred for CHD screening. The bigger proportion of these patients were from Kavango East and Omaheke region. Despite cardiac screening including echocardiography being mandatory in the first life of all neonates born with Down Syndrome (Al-Biltagi, 2013), findings of this study indicate that majority of these cases presented to paediatric cardiology clinic only when in heart failure. This could be because patients were either missed or not referred at an earlier age for cardiac screening. This stresses the importance of early referral to cardiac clinics. This finding is similar to a study conducted in Turkey, by Nisli et al where the most common single defect in down syndrome babies was AVSD (34.2%), followed by second Atrial Septum Defects (16.7%) and Ventricular Septal defects (16.5%) (Nisli et al., 2008). It is also consistent with another study by Aziz et al that found AVSD (67%) to be the most prevalent congenital heart lesion in Trisomy 21 children (Aziz et al., 2020).

Only 14% of cases with AVSD received cardiac surgical intervention and none of them received it within the first year of life. Almost a quarter of AVSD cases were pulmonary hypertensive and or were Eisenmenger receiving palliative medical care. Increased awareness is needed in order to provide early diagnosis of AVSD and prompt surgical intervention.

Genetic studies though limited, had a high likelihood of a positive result indicating a need for routine genetic screening in children with congenital heart disease (Ekure et al., 2018).

There are a number of limitations in our study, such as the fact that the figures reported herein are not population based, and any patients with CHD who died at home or at other hospitals and had never been diagnosed with AVSD were not included.

Moreover, patients who were diagnosed in previous years and failed to follow up for consultation, we were unable to accompany the presented figures with any surgical results. Irrespective of these limitations, we believe that we have made some progress in documenting the clinical epidemiology of AVSD among children at Windhoek Central Hospital.

5.3 Conclusion

The conclusions of the study were based on the discussions and objectives stated below:

5.3.1. Determine the incidence of children with AVSD aged between 0 to 12 at WCH between 2015 to 2020

It was found that the incidence of AVSD at Windhoek Central Hospital was 0.22 per 1000 live births. This figure was noted to be close to the incidence of AVSD in a general population in literature.

5.3.2. Determine the factors associated with children aged 0 to 12 diagnosed with AVSD at WCH between 2015 and 2020

Factors such as sex, prematurity and being syndromic were some of the factors investigated in this study. In regards to sex, the study found that males babies were affected as much as female babies. The study also revealed that babies born prematurely were more likely to be born with AVSD than babies born at full term. The researcher also went further to study at the age at which the diagnosis of AVSD is made and the regions with AVSD cases. The researcher found that bigger proportion of patients whose diagnosis of AVSD was made between ages of 6 weeks and 6 months.

In relation to sex, the binary logistic model revealed that sex is not a significant risk factor for AVSD among children with congenital heart disease. This is the case, despite a higher proportion of female children (52% female to 39% male) found to have AVSD.

Results from the study revealed that prematurity was a significant risk factor (AOR = 1.860, 95%: 0.99–3.463) for AVSD.

The study identified syndromic children among those diagnosed with AVSD, namely Down Syndrome and Noonan syndrome, however none of them were found to be a significant risk factor for AVSD (AOR = 0.120, 95%: 0.070 – 0.206).

5.4 Study Limitations

The results of this study should be interpreted considering that this is a single center data analysis. Although, this center drains from all corners of the country and the duration of the study being relatively long, the sample population may not be an accurate representation of the population at large. There could be a considerable amount of congenital heart patients who were never referred for proper diagnosis and management at paediatric cardiac clinic. Another potential limitation is that the study might have underestimated the burden of atrioventricular heart defect as only cases with clinical diagnosis and treated at the cardiology department were included. Nonetheless, the findings shed light on the burden during the five years reviewed and relevant recommendations were made for future research.

No single congenital heart disease, in particular atrioventricular heart defect was diagnosed antenatally (during pregnancy) in this study.

There was no information related to usage of alcohol, smoking, rubella infection during pregnancy or taking certain medication during pregnancy by the mothers to the

children born with AVSD. Additionally, information related to children born with AVSD to diabetic mothers was also not available. This type of information could have shed more light on the risk factors associated with AVSD.

Genetic studies were only done on children who appeared frankly syndromic, children with subtle dysmorphic features were not done genetic tests hence it is possible that the data from the study might not be accurate.

Furthermore, only mortality has been listed but close follow-up on the patients could shed more light on outpatient and late mortality as well.

5.5 Recommendations

After the discussions and conclusions, the researcher made the following recommendations:

5.5.1 Ministry of Health and Social Services

Paediatric cardiac care services are highly specialized; therefore, it is imperative that antenatal care professionals including midwives and junior medical officers, primary health care providers and pediatricians to have increased awareness of congenital heart disease.

1. To implement and support screening programs targeting CHD such as prenatal screening guideline and pulse oximeter screening in the newborn baby prior to discharge. This program to be implemented at all district hospitals with maternity units.
2. To conduct biannual training on neonatal examination to antenatal care providers such as midwives, junior medical officers and pediatricians who are in direct contact with newborn babies.

3. Extend outreach programs to the hospitals in the peripheral areas such as hospitals in Kavango east, Ohangwena and Oshana region where a high number of congenital heart diseases are being referred from. This is in order to raise CHD awareness, provide education to local health professionals and screen children for structural heart disease.
4. Implement an exchange program for health care professionals working at the peripheral hospitals, in order for health workers interested in paediatric cardiology get a chance to work at the paediatric clinic and cardiac unit at Windhoek Central Hospital for a period of 3 to 6 months.
5. Provide ECG machines to local hospitals and provide basic training to local health professionals as ECG, together with clinical examination and chest X-ray assist in the early diagnosis of congenital heart disease.
6. Human resources are the most valuable assets, hence there is a great need for healthcare workers to be trained, sustained and retained to continue serving the greater nation. Currently, cardiology department and in particular paediatric department is faced with the highest turnover of healthcare workers. Health professionals working in this department are faced with burnout, hence they do not stay long in the department.
7. To establish a national register and policy for Congenital Heart Diseases.

5.5.2 Research

There is need to conduct research on the clinical epidemiology and factors associated with other congenital heart diseases other than AVSD Namibia. It would also be good to include information such as age, use of alcohol during pregnancy and consanguinity of the parents, in order to study associations related to such factors as they are known

in general literature. Such information would improve the awareness and help the ministry of health and government at large in prioritizing paediatric cardiac services.

5.7 Summary

In this chapter discussions, conclusions, limitations and recommendations were drawn based on the three main objectives of the study. Interpretations were made to give meaning to the data after analysis with conclusions and recommendations drawn based on the study's major findings.

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Annexure 1: Data Collection Tool for Paediatric Congenital Cardiac Patients (AVSD)

SECTION A:

Anonymous number: Folder no: Date of consultation:

DOB: Age: Region: Sex:

SECTION B:

Diagnosis: (Age at first diagnosis)

General Examination: Cyanosis: 1. Yes 2. No Clubbing: 1. Yes 2. No

Blood pressure: Pulse: Saturation: Weight: Height:

Cardiac Examination:

Cardiac impulse/thrills: 1. Yes 2. No Heart sounds / murmurs: 1. Yes 2. No

Examination of other systems/Comobidies:

Respiratory system: 1. Normal 2. Abnormal Abdomen: 1. Normal 2. Abnormal

Neuro developmental system: 1. Normal 2. Abnormal Electrocardiogram: 1. Normal
2. Abnormal

SECTION C:

Echocardiogram: Cardiac catheterization:

SECTION D: Conclusion (Outcome):

Surgery done: a- Yes (When, age at surgery)

b- No

1. Patient doing well (successful operation)

2. Patient in failure

3. Patient needs re-operation

4. Patient for palliative

care

Annexure 2: Ethical Clearance Certificate



ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: DEC OSH 0004 **Date:** 04/04/2022

This Ethical Clearance Certificate is issued by the University of Namibia Ethics Committee (REC) 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 ethics committee.

Title of Project: CLINICAL EPIDEMIOLOGY OF ATRIOVENTRICULAR SEPTAL DEFECTS AMONG CHILDREN AT WINDHOEK CENTRAL HOSPITAL, 2015-2020

Principal researchers: LAHJA NDAPEWA IPINGE

Staff Number/ Student number: 200503669

Remarks: Low Risk - Approved with corrections

Centre for Research Services

Take note of the following:

1. Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the ethics committee. An application to make amendments may be necessary.
2. Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the ethics committee
3. The Principal Researcher must report issues of ethical compliance to the ethics committee (through the Chairperson) at the end of the Project or as may be requested by the ethics committee
4. The ethics committee 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.

The ethics committee wishes you the best in your research.

A handwritten signature in black ink, appearing to be 'Hans J Amukugo', written over a horizontal line.

Prof Hans J Amukugo (Chairperson Decentralized Ethics Committee)

A handwritten signature in black ink, appearing to be 'Davis Mumbengegwi', written over a horizontal line.

Prof. Davis Mumbengegwi (Head, Multidisciplinary Research)

Annexure 3: Permission letter to conduct the study from the Ministry of Health and Social Services



REPUBLIC OF NAMIBIA

MINISTRY OF HEALTH AND SOCIAL SERVICES

Ministerial Building
Harvey Street
Private Bag 13198, Windhoek

OFFICE OF THE EXECUTIVE DIRECTOR

Tel: No: 061 -203 2507
Fax No: 061-222 558
Andreas.Shipanga@mhs.gov.na

Ref: 17/3/3/ LNI
Enquiries: Mr. A. Shipanga

Date: 09 May 2022


Dr. Lahja N. Ipinge
PO Box 1704
Windhoek
Namibia

Dear Dr. Ipinge

Re: Clinical Epidemiology of Antrioventricular Septal Heart Defects among children at Windhoek Central Hospital, 2015-2020.

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 purpose;
 - 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.
4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,


BEN NANGOMBE
EXECUTIVE DIRECTOR

All official correspondence must be addressed to the Executive Director.



**Annexure 4: Data Collection Permission letter from Windhoek Central Hospital
Chief Medical Superintendent**

9-0/0001



REPUBLIC OF NAMIBIA
Ministry of Health and Social Services

Private Bag 13215
Windhoek
Namibia

Windhoek Central Hospital
Harvey Street
Windhoek

Tel. No: (061) 203 3024
Fax No: (061) 228886

Enquiries: Ms. S. Ipinge

Ref.17/3/3/LNI

Date: 02 June 2022

OFFICE OF THE CHIEF MEDICAL SUPERINTENDENT

Dr.Lahja N. Ipinge
P.O.BOX 1704
University of Namibia
Windhoek
0812747630

Dear Dr.Ipinge

**SUBJECT: PERMISSION TO COLLECT SECONDARY DATA FOR A STUDY ON
ATRIOVENTRICULAR SEPTAL DEFECTS AT CARDIAC CLINIC, WINDHOEK CENTRAL
HOSPITAL**

1. Reference is made to your application to conduct the above-mentioned study.
2. This letter serves to inform you that permission has been granted for you to conduct a study at Windhoek Central Hospital, on the above mentioned subject as you have requested and does not include any remuneration.
3. Patient/Client's information should be kept confidential at all times.
4. Preliminary findings to be submitted as it is stipulated on your application upon completion of the study.

Thank you.

Yours sincerely

DR .D.I.UIRAB
CHIEF MEDICAL SUPERINTENDENT



"Your Health, Our Concern"