THE PREVALENCE AND CLINICAL CHARACTERISTICS OF AUTISM SPECTRUM DISORDER IN CHILDREN AGED 1-15 YEARS SEEN AT THE UNIVERSITY TEACHING HOSPITAL IN LUSAKA, ZAMBIA

By

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A dissertation submitted in partial fulfilment of the requirement for the award of the Degree of Master of Medicine in Paediatrics and Child Health

THE UNIVERSITY OF ZAMBIA

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DECLARATION

I hereby declare that this dissertation is a representation of my own work and has not been represented either wholly or in part at the University of Zambia or any other university.

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CERTIFICATE OF APPROVAL

This dissertation 'The prevalence and clinical characteristics of Autism spectrum disorder in children aged 1-15 years seen at the University Teaching Hospital in Lusaka, Zambia' of Dr Kafula Lisa Nkole has been approved as partial fulfilment of the requirements for the award of the degree of Master of Medicine in Paediatrics and Child Health

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication and the presence of stereotyped repetitive behaviours. Despite the increase in the global prevalence of ASD, few studies have been done in Sub-Saharan Africa. The prevalence of ASD in Zambia is not known. This study determined the prevalence of ASD and described the clinical characteristics seen in the diagnosed children at a tertiary hospital in Zambia. This was a hospital based, cross sectional study conducted in two stages (i) screening with an autism RED FLAG SYMPTOM CHECKLIST and (ii) diagnosis using the DSM V CRITERIA FOR ASD. It was conducted in the Paediatric out patients department, at the University Teaching Hospital in Lusaka, Zambia over an eight month period from May 2016 to January 2017. Five hundred and sixty participants were enrolled in this study. Fifteen children (2.6%) reported at least one red flag symptom. Of these, eight fulfilled the DSM V diagnostic criteria for ASD. Therefore, the prevalence of ASD in this study was 1.4 %. Common clinical characteristics seen in the children with ASD were male sex, age between 36-48 months and inability to utter a single word by the age of two years (non-verbal symptomatology). Paternal and maternal age above 30 years at the time of the child's birth and high parental education levels were the common socio-demographic characteristics seen in the group of children with ASD. The prevalence of ASD at this tertiary institution was 1.4 %. An increase in public awareness and knowledge of the early warning signs of autism and training of health personnel in the recognition, diagnosis and management of children living with ASD is warranted. Large scale population studies are needed to ascertain the national prevalence of ASD.

Key words: Autism, Prevalence, Hospital based, Zambia

DEDICATION

This work is dedicated to Theresa Grace Chabula Mushili, forever in my heart.

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ABBREVIATIONS

ADDMN: Autism and developmental disabilities monitoring network

ADI-R: Autism diagnostic interview – revised

ADOS: Autism diagnostic observation schedule

ASD: Autism spectrum disorders

CDC: Centre for disease control

CNS: Central nervous system

DIC: Developmental intervention clinic

DSM: Diagnostic and statistical manual

GABA: Gamma-amino butyric acid

GIT: Gastro intestinal tract

PCOE: Paediatric Centre of Excellence

PDD: Pervasive developmental disorders

PDD-NOS: Pervasive developmental disorders not otherwise specified

UTH: University Teaching Hospital

CHAPTER ONE: INTRODUCTION

1.1 Background

Autism Spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired verbal, non-verbal communication, restricted and repetitive behaviour and social interaction. The term autism is derived from the Greek term *autos* meaning self and was first used in the early 1900's by Eugene Bleuler when he described certain withdrawal symptoms in schizophrenic patients. In 1943, Leo Kanner, a psychiatrist, used the term for the first time to describe a group of children who had symptoms consistent with the diagnosis of autistic disorders in a paper entitled *Autistic disorders of affective contact (Kanner, 1943*). He described them as '*children's aloneness from the beginning of life*' in reference to the array of behaviours that he observed as being present at birth. Parents or guardians usually notice signs within the first two years of their child's life which develop gradually. However, some children with autism reach their developmental milestones at a normal pace and then regress. The degree of impairment and cognitive functioning varies from one individual to the next. Autism can present with lifelong challenges even in its mildest form.

Globally, autism is estimated to affect 24.8 million people as of 2015. As of 2010, the number of people affected was estimated at about 2–7 per 1,000 worldwide *(Hill et al, 2013)*. The number of people diagnosed has been increasing dramatically since the 1980s.

1.2 Screening and Diagnosis of Autism spectrum disorder

In 2000, Fillipek et al recommended a two level model for screening and diagnosis of developmental disabilities and ASD. The first level constitutes routine developmental surveillance and screening of all children for developmental disabilities and specifically for autism spectrum disorder. This identifies all children at risk of developmental delay and particularly ASD. Level two, involves an in depth clinical assessment of the high risk children and it identifies and differentiates children with autism from other developmental disabilities. Normative data from various standardized language instruments have been used to formulate conventional developmental language

milestones (*Fillipek et al, 2000). Therefore, the lack of acquisition of the following milestones within known, accepted and established ranges is considered abnormal: no babbling by 12 months; no gesturing (e.g., pointing, waving bye-bye) by 12 months; no single words by 16 months; no 2-word spontaneous (not just echolalic) phrases by 24 months; and any loss of any language or social skills in the early developmental age. These early warning signs are the internationally recognized red flags of autism (*Fillipek et al, 2000*). Several screening tools have been developed to improve the early diagnosis of ASD. These screening tools are age specific. The modified checklist for autism in toddlers (M-CHAT) is valid for children aged 16-30 months. The other tools include the STAT (screening tool for autism in toddlers and young children) and the autism screening quotient (ASQ) for children aged 24-36months and children aged 4 years and older respectively. These screening methods may however fail to adequately recognize milder cases of ASD.

The centre of the diagnosis of ASD has revolved around behavioural symptoms, impaired social interaction and communication and narrow range of interests. The concept of "spectrum" describes the continuum of impairment which may extend beyond clinical bounds to those with combinations of milder social abnormalities and communication impairment and less rigid interest restrictions *(Bailey et al, 1998*). Until recently, the *Diagnostic and Statistical Manual of Mental Disorders*, fourth revision (DSM- IV) criteria for diagnosis of autism was used to make the diagnosis of autistic disorders. This encompassed autism disorder, asperger's disorder, child disintegrative disorder, and PDD NOS as separate specific diagnoses. In 2013, a new criterion was released under *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition (DSM-V) which encompassed all the PDDs into a single diagnosis called Autism spectrum disorder. This was supported by some scientific evidence that a single diagnosis better reflects the symptomatology, the evolution of the disorder and the clinical responses.

The DSM-V in comparison to the DSM-IV combined the deficit in interaction and communication and into one core symptom. These symptoms should be present in the early developmental period even though they may manifest later in life and must cause

clinically significant impairment in social, occupational or other important areas of current functioning. Children with autism have a severe lack of interest in things and people around them as evidenced by their incapability to carry out a meaningful conversation with other people and the inability to use gestures as a means of communication. Early intervention with behavioural, communication, and occupation therapy may help with their day to day living.

Changes made to the criteria from the DSM–IV to the DSM-V brought about a lot of questions and uncertainties pertaining to the validity and reliability of the DSM-V. These criteria showed excellent specificity (*Frazier et al. 2011, Mattila et al. 2011, McPartland et al. 2012*), however the new criteria was thought to be too restrictive by some researchers and clinicians (*Gibbs et al. 2012; McPartland et al. 2012, Matson et al. 2012a, 2012b)*. Some reports have indicated that 60% or fewer of those with DSM-IV ASD diagnoses would satisfy DSM-5 criteria, and in this regard many questions have been raised about individuals diagnosed with Asperger's disorder or Pervasive developmental disorders not otherwise specified (PDD-NOS) under the DSM-IV diagnostic criteria and those with normal cognitive function and better developed verbal abilities. These groups have especially showed very low sensitivity rates (*Matilla et al. 2011; McPartland et al.2012)*.

Prior to the introduction and adoption of the new criteria, field trials on the DSM-V for different selected diagnosis were done by Darren *et al* in 2013 at eleven sites across the United States and Canada. Their main objective was to obtain precise (standard error <0.1) estimates of the intra class kappa so as to determine the degree with which two independent raters agree on the presence or absence of selected DSM- diagnoses, when the same patient was interviewed on separate occasions, in clinical settings, and evaluated with usual clinical interview methods. Using the DSM-V, autism spectrum disorder showed very good test and retest reliability. Of the two sites where ASDs were tested, one site showed no significant change in prevalence rates between DSM-IV and DSM-V groups while there was a slight reduction in the DSM-V autism spectrum rates at the second site. The combined prevalence rates of DSM-IV autistic disorder, asperger's disorder, and pervasive developmental disorder not otherwise specified in the

clinic population at the two sites were 0.23, and 0.26 respectively. However, based on DSM-5 criteria, the prevalence rates were 0.24 (95% CI=0.20–0.30) and 0.19 (95% CI=0.15–0.24) respectively *(Darren et al, 2013)*.

Other commonly used tools in the diagnosis of ASD, are the Autism Diagnostic Observation Schedule (*ADOS; Lord et al. 1999)* and the Autism Diagnostic Interview – Revised *(ADI-R; Rutter et al. 2003).* The diagnostic algorithms for the ADOS and ADI-R were designed to maximize sensitivity and specificity based on DSM-IV. In a study done by *Mazefsky et al* in 2014, an algorithm for mapping ADOS and ADI-R items onto the DSM-5 was developed. There was a significant variation in the percentage of participants satisfying all DSM-5- requirements according to the data from the Autism Diagnostic Observation Schedule (ADOS; 33%) group versus Autism Diagnostic Interview-Revised (ADI-R; 83%) group. This highlighted the impact of diagnostic methodology on ability to document DSM-5 symptoms. However the combined utilization of both the ADOS/ADI-R data revealed that 93% of participants met DSM-5 criteria. This can infer the likely continuity between DSM-IV and DSM-5 research samples characterized with these instruments in combination (*Mazefsky et al, 2013*).

Data on common symptoms (patterns) and risk factors for ASD in Zambia is scarce. However in 2008, the first Developmental intervention clinic (DIC) was opened at the Paediatric Centre of Excellence (PCOE) at the University Teaching Hospital. Its sole purpose is to offer multi-disciplinary assessment and early intervention for children with developmental delay and / or neurological disorders. This centre offers both group and individual therapy for these children. These activities are aimed at increasing functional communication, social skills, sensory integration, activities of daily life and minimizing challenging behaviours. The DIC also helps create a network with other associations or educational partners working with children with ASD. Currently the DIC team offers the following specialty services, paediatric neurology, physiotherapy, occupational therapy, speech therapy, behaviour support, psychosocial counselling, child neuropsychology (cognitive assessment and learning support). Currently, children with ASD account for about 16% of children seen in the DIC, with 124 patients in active treatment between 2013 and 2016.

A lot of research has gone into developing new screening and diagnostic tools that can improve the detection of ASD with the aim of improving the quality of care provided to the affected individuals. Early detection and intervention may improve the neurological outcome and quality of life of the affected individuals. Hence, estimation of the true prevalence can help in planning diagnostic and intervention services for affected children.

1.3 Statement of the Problem

Currently the prevalence of ASD in Zambia is unknown. Undiagnosed and/or misdiagnosed children with ASD will not receive any intervention. This may have social and economic implications on their families and communities. Early detection and intervention may help equip this group of individuals with social, communication and behavioural skills needed for them to lead independent lives with some of them getting formal employment in adulthood. Although literature reveals that there is an increase in the prevalence of autism spectrum disorder worldwide, the extent of the burden in Africa particularly in Zambia still remains obscured as no recent hospital-based, population or community studies were identified in literature. This study aimed at determining the prevalence of autism spectrum disorder among children who presented to the paediatric department of the University Teaching Hospital in Lusaka, Zambia and to describe the common presenting clinical characteristics in children with ASD.

There is a lack of diagnostic and educational services for individuals living with autism in Zambia. Most of the government operated special schools combine all the children with disabilities in one class. Most children with autism require unique teaching strategies and environment. The findings of this study may help increase awareness about the burden of ASD and promote early identification and intervention of children with autism spectrum disorder as this plays a pivotal role in the prognosis of this condition.

1.4 Research question

1. What is the prevalence of ASD in children aged 1-15 years seen at the Paediatric outpatient department of University Teaching Hospital in Lusaka, Zambia?

2. What are the most common clinical characteristics of autistic children seen at the Paediatric outpatient department of University Teaching Hospital in Lusaka, Zambia?

1.6 General objective

To determine the prevalence and the most common clinical characteristics of ASD in children aged 1-15 years seen at the University Teaching Hospital, in Lusaka, Zambia.

1.7 Specific objectives

1. To determine the proportion of children with ASD in children aged between 1 and 15 years seen at the University Teaching Hospital using the Diagnostic Statistical Manual of Mental Disorders, 5th edition (DSM V).

2. To describe the clinical characteristics of autism in children aged between 1 and 15 years seen at the University Teaching Hospital.

3. To determine the proportion of children with ASD and other neurological co-morbid conditions.

CHAPTER TWO: LITERATURE REVIEW

2.1 Descriptive Epidemiology of ASD

The global prevalence of ASD according to WHO is about 1 in 160 people. This accounts for about 0.3% of the global disease burden (*WHO autism report, 2013*). The latest surveillance data by Centres for Disease Control (*CDC*) done in USA shows that 1 in every 68 children aged 8 years old has ASD. The prevalence of ASD in the United States has increased from 1 in 150 children in 2002, to 1 in 68 children (14.7/1000 children) in 2012 *(Christensen et al,2012)*. The increase in prevalence may be attributed to the substantial growth in research surrounding the area of autism. This has been driven by the increase in the recognition, awareness and understanding of ASD among educational and clinical professionals and the population at large. Other reasons include changes in study methodology, an increase in possible autism risk factors and the increase in rates of acceptance that autism can coexist with a range of other medical conditions *(Williams et al, 2006)*. According to a systemic review of prevalence studies on autism spectrum disorder done by William *et al* in 2006, the overall random effects estimate of prevalence across studies of typical autism was noted to be 7.1 per 10,000 and of all ASD were 20.0 per 10,000 (0.2%). It has been recorded that ASD occurs in all ethnic, racial and socioeconomic groups (*Christensen et al,2012)* and it affects more boys (1 in 42 children) than girls (1 in 189 children) with a ratio of 5:1, with the diagnosis being made between the ages of two and six years *(Christensen et al,2012)*. Severity of ASD is determined by the severity of impairments in communication, social interaction, perception and processing of information and how this affects their daily living.

Population-based ASD prevalence studies worldwide reveal extensive heterogeneity *(Hill et al, 2013).*). Studies done from the year 2000 onwards have shown great variability in the prevalence rates. The variability in study population, study design considerations, case definition all play a role in the inferences about prevalence and trends that can be made from these studies.

There has been significant variation in prevalence rates in some European countries (Sweden, Denmark, UK, Iceland) ranging from 1.9/10 000 to 72.6/10 000 with a

median value of 10.0/10 000 (**0.1%**) which may also be attributed to differences in the study methodologies used and the imperfect sensitivity of case ascertainment (*Elsabbagh et al, 2012*). This may reduce the overall prevalence rates seen in some of the studies. Swedish studies investigating the prevalence of ASD among children of mothers of Somalian and Ugandan origin observed a higher prevalence of ASD in these children compared to other children in the general population (0.7% and 0.2% respectively).

Japan and China provide the most comprehensive studies done on ASD in the western pacific region. The recent Korean study done by *Kim et al* showed the highest rate to date of 189/10 000 (1.89 %) among children aged 7-12 years attending regular main stream school(*Kim et al, 2011*). This was followed closely by a Japanese study done in 2008 by Kawamura et al (*Kawamura Y et al,2008*) which revealed a prevalence rate of 181.1/10 000.(1.81%). In China, *Wong and Hui* in 2008 recorded a low estimate of 16.1/ 10 000 (0.16%).

The earliest ASD prevalence studies in Africa date back to the 1970's. Victor Lotter described autism among children with mental handicap for the first time, in six central and southern African countries (Nigeria, Ghana, Zimbabwe, Zambia, Kenya and South Africa) and found a rate of 1 in 145 children (*Lotter V, 1978*). Cultural factors, societal acceptance of the condition, availability of services and existence of national or state funded treatment options may be some of the factors that affect the identification of clinical characteristics, diagnosis, and treatment of ASD in this region (*Bernier et al, 2010*). The prevalence of autism spectrum disorder in children with disabilities is higher compared to that seen in the general population. Seif Eldin *et al* studied the prevalence of autism spectrum disorder among children with developmental disorders in the Arabic population and included two African countries that had a majority Arab population. These countries, Egypt and Tunisia had prevalence rates of ASD among children of 33.6% and 11.5% respectively (*Seif Eldin et al, 2008*). A clinic based population study done over a period of one year in south eastern Nigeria in 2011, revealed a prevalence rate of 0.08% (*Bakare OM et al, 2011*). Literature search did not reveal any large scale

epidemiological studies done in Africa as a follow up to the one done by Victor Lotter over four decades ago.

2.2 Aetiology and pathophysiology of Autism Spectrum disorder

The cause of autism remains unknown but many aetiological factors have been postulated. Understanding the theories and concepts that surround the aetiologies of autism spectrum disorder is important. There has been an evolvement of these theories over the years with recent studies now focusing on the genetics of autism. Recent scientific evidence shows a diversity of morphological, functional, genetic and neurotransmitter system alterations (*Polsek et al,* 2011).The aetiology of autism is thought to be multifactorial with both genetic and environmental factors playing a role. The plasticity of the brain in early infancy may allow for post natal factors to affect the natural history of ASD, despite the predominant prenatal aetiology (*Polsek et al, 2011*). Despite it being a brain pathology, no single model of pathophysiology is currently accepted, as no specific distinguishing neuro-pathologic features that have been identified. Several physiologic abnormalities have been reported, hence the reference to them as a spectrum disorder.

Understanding the neuropathology of autism requires understanding the functional role of the major brain regions thought to be involved in this disorder and how they relate to the core behavioural symptomatology seen in the autistic spectrum. Dysfunction of one particular area of the brain has not been shown to be a direct cause of autism, rather, the interplay of many areas of the brain resulting in similar behavioural consequences has been proposed. Autopsy investigations have suggested subcortical and/or forebrain anomalies in the limbic system or in the cerebellum in patients with autistic disorder (*Kemper TL et al, 1998, Carper RA et al, 2002).* Reduced numbers of Purkinje cells in the cerebellum and abnormalities in brainstem nuclei have also been replicated across autopsy and imaging studies (*Kemper et al, 1998, Courchesne, 1995*). Other functional imaging studies of persons with ASD have called particular attention to both the amygdala and the fusiform gyrus, a structure apparently important in the recognition of faces though more replication is needed. *(Grelotti DJ et al, 2002*).

A lot of research has focused on the alteration of several neurotransmitters in autism. Unfortunately none of these findings have provided a conclusive causal theory .Of the important neurochemical theories supported by diverse research, the excitation/inhibition imbalance theory based on glutamate and gamma amino butyric acid (GABA)-related abnormalities is one of the most important ones. It has been hypothesized that a complex lack of local inhibition and long distance excitation during early development and in later life could be common factors to the developmental findings in autism (*Polsek et al,* 2011). Serotonin plays a role in regulating behavioural, autonomic and cognitive function (*Murphy and Lesch 2008*), and in prenatal neurodevelopment *(Di Pino et al, 2004*). Findings of consistently higher than normal serum levels of serotonin in autistic patients has been replicated in several studies. These finding connect serotonin dysregulation to the possible aetiology of ASD. A study done by Leboyer *et al* in 1999 found 29 of 60 autistic individuals (48%) with elevated levels of serotonin. This elevation was not dependant on age. A systematic review of 22 studies done by Gabrielle *et al* in 2014 revealed that elevated levels of serotonin were recorded in 28.3% in whole blood and 22.5% in platelet rich plasma samples of individuals with autism in 15 and 4 studies respectively. No correlation between the severity of clinical findings and the serum level of serotonin has been established. However in 2010, Kolevzon et al found an inverse association between low whole blood levels of serotonin and aggressive behaviour towards self (*Kolevzon et al, 2010).*

Environmental and genetic factors have been thought to interact, ultimately increasing the risk of developing ASD. There is an estimated 60% to 92% concordance rate in monozygotic and 0% to 10% rate in dizygotic twins (*Dukin et al, 2008)*. Familial aggregation of ASD in sibling and population-based studies supports the large heritability estimates found in the twin to twin studies. Although the heritability of autism has been estimated to be as high as 90%, the genetic factors are heterogeneous and complex and have been poorly understood. Studies done in twins, families and in children with rare chromosomal disorders suggest that heritable factors play a substantial role in autism spectrum disorder. However, although multiple genes have been identified, no specific genes have been demonstrated to cause autism. Several

studies are presently underway to describe the precise mechanism of genetic inheritance of autism. These are being explored through methods of genome wide screening, cytogenetic studies, and evaluation of candidate genes *(Belhadj et al, 2006)*. Some genetics studies have identified four major chromosomes that possibly play a role in the aetiology of autism spectrum disorder. According to the international molecular genetic study of autism consortium, the identified chromosomes are numbers 2, 7, 16 and 17. Chromosome's 7 and 2 are known to be associated with many language disorders and play an important role in early brain development respectively *(Ganaie et al, 2014)*. Several studies done have estimated that the probability of autism spectrum disorder in siblings of ASD cases is between 2-6%, but can be as high as 7%. Siblings of ASD cases have ten times more risk of developing ASD than general population (*Ganaie et al, 2014).*

A variety of non-heritable risk factors have been associated with developing autism spectrum disorder. No single factor has been implicated as a direct cause of autism. It appears that these factors are all associated with disruption of the normal function of the brain and that may occur in the pre natal period. Selected studies done on non-heritable factors associated with autism cited maternal infection and maternal drug use as common risk factors. Prenatal viral infections account for the major non- heritable cause of autism spectrum disorders *(Piven. J et al, 1993)*. In 1977, Chess reported that 8-13% of children born in the 1964 rubella pandemic went on to develop autistic features together with the other birth defects associated with congenital rubella syndrome. Other infectious agents implicated were maternal cytomegalovirus infection, toxoplasmosis, varicella zoster, and rubeola and herpes simplex viruses. Published literature of these other infectious pathogens has comprised of only a few case reports. A nationwide study done in Denmark in 2010, that looked at all children born from 1980 through to 2005 concluded that maternal viral infection in the first trimester and third trimester maternal bacterial infection were associated with an increased risk of ASD in the offspring (*Atladottir et al,2010*). Nationwide registers were used to obtain the diagnosis of ASD and maternal infections.

Prenatal use of certain medications like thalidomide, valproate and other anticonvulsants has been postulated to be associated with an increased risk of children developing autism. According to a study done by Stromland *et al* in 1994, prenatal thalidomide ingestion during days 20–24 of gestation has been associated with an increased risk for autistic disorder and this strongly suggested that early prenatal xenobiotics could play a role in ASD aetiology. Evidence from both animal studies and cases reports indicate that valproate use in pregnancy has been shown to increase the risk of developing autism spectrum disorder. (*William G et al, 2001)*. Little evidence exists supporting any one heritable risk factor as being an independent risk factor. This can be attributed to the fact that none of the studies done were population based studies and have not been adequately sized to detect significant effect (*NewSchaffer et al, 2002*). Advanced parental age has been shown to increase the risk of having a child with autism spectrum disorder (*Dukin et al, 2008*). While there has been an association between prenatal alcohol exposure and an increased risk of autism in the offspring, no significant association was observed between the two in a Danish study involving 80 552 children and their mothers *(Pickler et al 2009, Elliasen et al,2010).* Low birth weight and being small for gestational age may increase the risk of ASD however; there is insufficient evidence to implicate any one of these risk factor as a cause of ASD (*Gardener et al, 2009*).

Some of the aetiological hypotheses proposed by literature coming from Africa include post-encephalitic infections or sepsis preceding the onset of autism spectrum disorder like symptoms, genetic factors, auto-immune factors, and vitamin D deficiency. Mankosi *et al* in a case series done in 2006 documented cases of autism symptomatology following post-encephalitic infection/sepsis in a population of children from Tanzania (*Mankosi et al 2006*).

2.4 Symptomatology of Autism spectrum disorder

The core symptoms of ASD include impairments in social interaction, communication and restricted, repetitive repertoire of behaviour. Children with ASD will often have abnormalities in social approach and inability to carry out normal back-and-forth conversation, reduced sharing of interests, emotions, or affect and failure to initiate or

respond to social interactions (*American association of psychiatry, DSM-V*). They may also often present with abnormalities in nonverbal communicative behaviours used for social interaction like abnormalities in eye contact and body language or problems in understanding and use of gestures to total lack of facial expressions and nonverbal communication(*American association of psychiatry, DSM-V*). Deficits in developing, maintaining, and understand relationships is another a common symptom of ASD. This may include problems adjusting behaviour to suit various social contexts, difficulties in sharing imaginative play or in making friends and often, absence of interest in their peers.

Repetitive behaviours may include, stereotyped or repetitive motor movements (simple motor stereotypes like hand flapping or rocking), use of objects like lining up toys or flipping objects or irregularities with speech (echolalia, use of idiosyncratic phrases). Individuals with ASD may insist on adhering to the same routines, or have ritualized patterns of verbal or nonverbal behaviour. Children with ASD have difficulties with transitioning from one situation/environment to the next and may experience extreme distress at small changes. They may also have highly restricted and fixated interests that may be abnormal in intensity or focus. This may include excessive preoccupation with unusual objects and circumscribed or repetitive interests (*American association of psychiatry, DSM-V*). Other features of ASD include increased or reduced reactivity to sensory input or unusual interest in sensory aspects of the environment. This may include apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement (*American association of psychiatry, DSM-V*).

Autism is a disorder that usually begins in infancy, at the latest, in the first three years of life. Social deficits may not be immediately obvious in the early years but may become more obvious when the child becomes mobile and more sociable. Several factors may affect the age at which parents recognize symptoms and ultimately the age at which diagnostic assessment and intervention are sought. Chawarska *et al* in 2006 examined the factors related to parental age of recognition (AOR) of early abnormalities and its association to diagnosis and levels of functioning at 2 and 4 years in 75 toddlers

with ASD. Maternal age and early social and motor delays were among the factors associated with parental age of recognition. The authors found that higher maternal age was associated with later age of recognition.

Lotter in 1980 documented that the pattern of stereotypic repertoire of behaviour was observed to be less common among African children compared to children in the West. Lack of expressive speech has been observed to be the commonest presenting symptom in Africa (*Belhadj et al 2006).* Belhadj *et al* found that 51.2% of the cases of ASD seen in their clinic were non-verbal cases (*Belhadj et al, 2006*). Similarly, Mankosi et al in 2006 reported 71 % of non- verbal cases of ASD in their study. They attributed this to the local diagnostic practices and concluded that African children with non-verbal symptoms are more likely to seek medical attention as compared to children with verbal symptoms (*Mankosi et al, 2006).*

In 2007, American academy of pediatrics recommended that all children should be screened for developmental delays and disabilities during regular well child visit at 9, 18, 24 or 30 months. Additionally all children should be specifically screened for ASD with an ASD specific screening tool at 18 and 24 months. This allows for early diagnosis and institution of early intervention.

2.5 Co- morbid conditions associated with autism spectrum disorder

Various conditions co-morbidly occur with autism spectrum disorder. The common associated developmental disorders include verbal learning disorders, Attention deficit/hyperactivity disorders (ADHD), intellectual disability, motor impairments, epilepsy, sleep dysfunction and anxiety *(Mannion and Leader, 2013).* According to data compiled in the United States by the CDC in the 2008 ADDMN, approximately 38% of children with ASD had intellectual disability (IQ less than 70 or examiners statement of intellectual disability), with 24 % of children with borderline range of IQ between 70-85% and 38 % of children had an IQ of above 85%. ADHD is a disorder of hyperactivity, impulsivity, inattentiveness. An American study done by Rao and Linda in 2013 looked at school going children aged 4-8 years with ASD and ADHD and concluded that compared to children with ASD only, these children had lower cognitive functioning, more severe impairment and greater delays in adaptive functioning (*Rao et*

al, 2013). Leitner's review in 2014 of 35 ASD and ADHD "co-occurrence" studies yielded estimates between 37% and 85%. Thirty one per cent of children with ASD in small community based study of 109 children from Boston and Salt lake city which looked at comorbid psychiatric disorders in children with ASD, had ADHD (*Leyfer et al 2006).*Stevens et al in 2015 looked at data drawn from a nationwide survey done in 2011 *(Pathways)* and found a co morbidity rate of ADHD and ASD of 59% (*Stevens et al, 2016).*

In Sweden, Carlston et al recently assessed 198 pre-school children with ASD aged 4.5-6.5 years for co morbid disorders and found that 78% had language problems, below average motor function in 37%, intellectual disability 49% and hyperactivity in 33% (*Carlston et al, 2013*). Epilepsy occurs in 10-30% of children with ASD (*Mannion et al, 2013, Tuchman, 2002*). A meta-analysis of 10-14 studies (1968-2006) of epilepsy in autism found that 21.4% and 8% of individuals with and without intellectual disability respectively, had epilepsy (*Amiet et al, 2008*).

Motor impairments commonly seen in children with ASD include stereotypies, motor delays and deficits, such as dyspraxia, incoordination and gait problems. Sleep dysfunction often presents as difficulty with sleep onset and prolonged awakenings during the night. (*Maski et al, 2011*). It has observed that intellectual disabilities occurred co-morbidly with autism spectrum disorder in over 60% of the patients in Africa *(belhaj et al, 2006*). This concurred with a study done in Tanzania by Mankosi *et al* which concluded that autism spectrum disorder among African children commonly occurred with intellectual disability. Other noted co-morbid conditions associated with autism spectrum disorder documented in Africa were epilepsy and oculo-cutaneous albinism.

There has been a demonstrable increase in the prevalence of ASD in the developed countries. Increased levels of knowledge and awareness, changes in study methodologies and improvement in the screening and diagnostic tools may account for this increase. More research is required to support this apparent increase and to explore the possible genetic and environmental risk factors of ASD in the developing countries.

CHAPTER THREE: METHODOLOGY

3.1 Study type

This was a hospital based cross sectional study conducted in the outpatient department of the Paediatric department, at the University Teaching Hospital in Lusaka, Zambia between May 2016 and January 2017.

3.2 Study site

The University Teaching Hospital is located in the city of Lusaka, Zambia. It is the highest tertiary institution in this southern African country. The paediatric out-patients department includes general and specialist clinics (clinic 2) and the emergency room (AO1). The outpatients department has an average annual attendance of about 25 000 children.

3.3 Study population

This included all children aged between 1-15 years who were seen in the Paediatric outpatient department at the University Teaching Hospital during the study period.

3.4 Sampling

Simple random sampling was done of patients that presented to the outpatient department. On each day, each patient was given a serial number and the patient numbers that correspond with the six random computer generated numbers was picked for the study. The study was conducted in the emergency room on Mondays and Tuesdays and out patient's clinic on Wednesday's, Thursday's and Friday's between 08:00hours and 16:00 hours for a period of eight months. The aim was to enrol a minimum of 6 children a day.

3.5 Sample size

There is a significant shortage of studies on both hospital and general population studies in Africa. The hospital based prevalence of ASD is expected to be higher than that seen in the general population. For that reason, the highest and latest general population prevalence of ASD (1.4%) done across the United States of America was used.

$$N = \underline{Z^2 \ X \ P(1-P)}$$

$(E)^2$

Where   N = sample required

Z = 1.96 (95% C I)

P= expected prevalence 1.47%

E= margin of error 0.01

Therefore, $N=\dfrac{1.96^2 X\ 0.0147(1-0.0147)}{(0.01)^2}$

=**556 children**

3.6 Eligibility criteria

Inclusion criteria

1.   All children aged 1-15 years who presented to UTH.

2.   Children whose parents consented to being part of the study

Exclusion criteria

The DSM V criteria for ASD point E states that the observed disturbances in social interaction, communication and behaviour should not be better explained by intellectual disability or global developmental delay. It is for this reason that the following children (1-4) were excluded from the study.

1. Children with previous central nervous system infection
2. Children with Cerebral palsy
3. Children with chromosomal disorders
4. Children with intellectual disability
5. Children whose parents did not consent to the study

3.7 Study procedure

The study procedure is shown in figure 1 below.

All children aged 1 to 15 years presenting to the University Teaching Hospital Paediatric department on the selected days were eligible to participate in the study.

Consent and assent (when required) was sought from all eligible participants.

Guardians that did not consent to the study were referred to the appropriate doctors for management of their child's presenting complaint.

Demographic and contact data was collected at the point of contact for everyone who consented to participate in the study.

Participants that consented to taking part in the study were then assessed for the following internationally recognized symptoms of (red flags) of ASDs:

❖ Any infant who did not babble or coo by age 12 months
❖ Any infant who did not gesture (point, wave, grasp, etc.) by 12 months of age
❖ Any child who did not say a single word by 16 months of age
❖ Any child who did not say two- word phrases on his or her own (rather than repeating what has been said to him or her) by 24 months of age
❖ Any child who had any loss of language or social skill at any age in the early developmental period.

Any child with any of the red flag symptoms was further evaluated using the DSM-V criteria for ASD to confirm the diagnosis of ASD. Participants from out of Lusaka were evaluated on the same day. Others were asked to return on another specific day for full evaluation. Upon their return, a questionnaire was administered to them. This questionnaire encompassed a focused history and examination.

Evaluation using the DSM 5 criteria involved Interaction with the child and parent/guardian to observe/elicit:

1) Deficits in Social communication and interaction with the investigator and the parents.
2) Any evidence of repetitive ,restricted patterns of behaviour (pertaining to speech, motor movements or any preoccupation with objects)

All children who fulfilled the case definition of ASD according to the DSM V criteria were then referred to DIC for further management.

All the data collected was filed and placed in a cabinet which was locked at all times to ensure confidentiality.
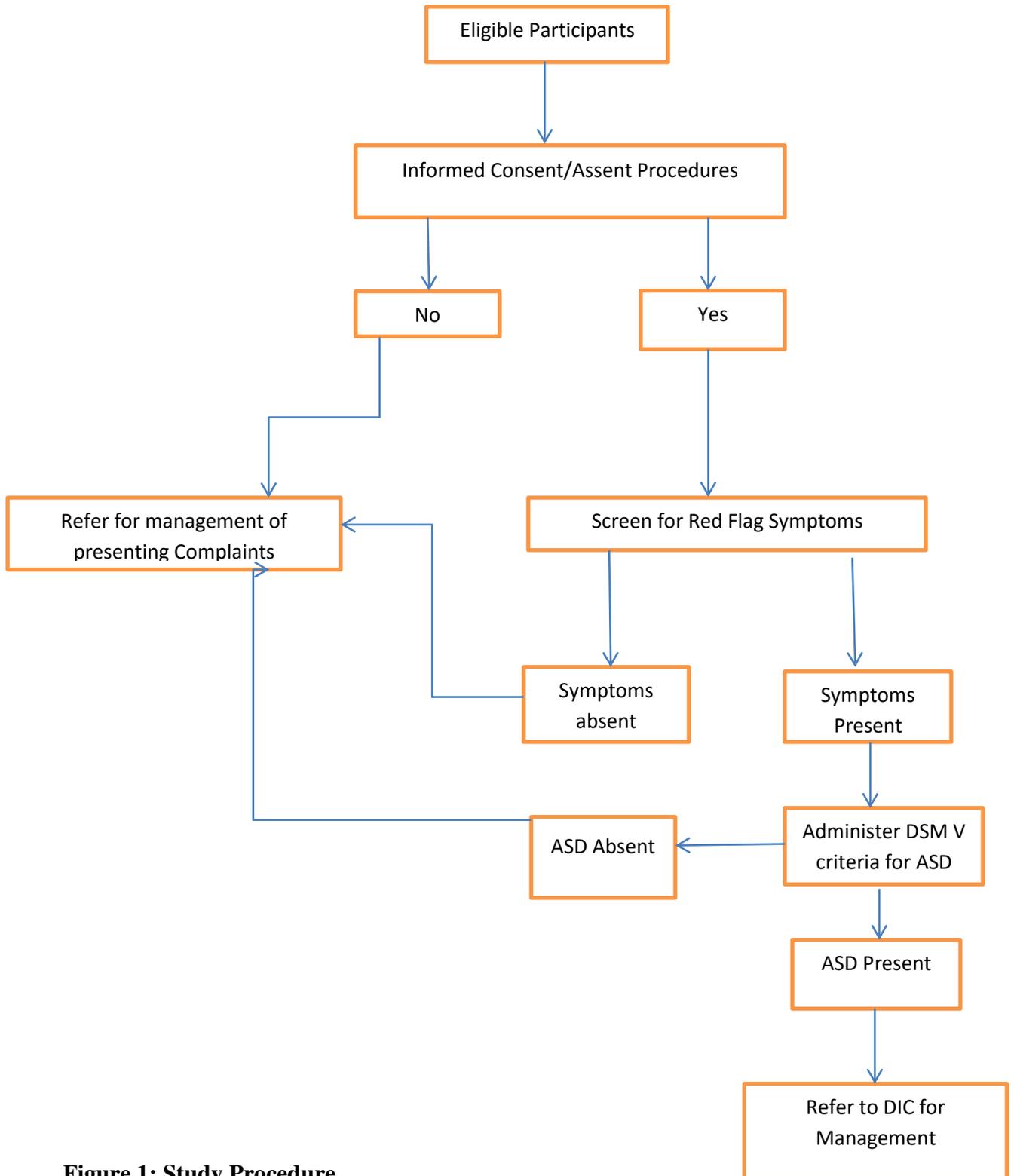
Figure 1: Study Procedure

3.8 Outcomes

Primary outcome

The proportion of children with Autism spectrum disorder as outlined by the DSM V criteria.

Secondary outcome

The proportion of children with ASD and other Co-morbid conditions like epilepsy, motor impairment, and Attention deficit hyperactivity disorder (ADHD), sleep disorders.

Confounding factors

•   Other Medical conditions

3.9 Independent Variables

- Sex
- Age
- Sibling with Autism spectrum disorder
- Co –morbid conditions like epilepsy
- Maternal age at child's birth
- Paternal age at child's birth
- Birth weight
- Maternal antenatal infection
- Maternal drug use

3.10 Data management

A standardized data entry questionnaire for each research participant was used for data collection. The collected data was then entered and analysed using SPSS version 17.

3.11 Descriptive statistics

The primary outcome as outlined above was to determine the prevalence of the children with the ASD according to the DSM V criteria.

Proportions and percentages were used to describe any categorical variables like sex, maternal antenatal infection, and presence of co-morbid conditions and outcome (the percentage of children with Autism spectrum disorders). Means and medians were used to describe continuous variables. These were presented as tables, charts and graphs.

3.12 Analytical statistics

Chi square test was used to determine the association between the independent variables (sex, maternal age at birth, paternal age at birth) and the dependent variable (if the children had ASD or not).

3.13 Ethical considerations

Ethical clearance was obtained from ERES CONVERGE IRB (REF NO: 2016-JAN-012). Permission to conduct the study was requested from the administrative management of the University Teaching Hospital.

The purpose and procedures of the study was clearly explained in the language preferred by the parent/guardian and a written informed consent obtained. All data collected in this study was confidential and was only shared with attending doctors.

All children that met the criteria for diagnosis of autism spectrum disorder were referred to the appropriate specialists for multi-disciplinary management.

Emphasis was made that participation in the study was voluntary and that participants were free to withdraw from the study at any point.

The risks and benefits of the study were fully and clearly explained to the participants as described in the consent form. Parents, who had difficulties accepting and adjusting to their child's new diagnosis of ASD, were referred to an appropriate psycho-social councillor. Children with ASD had expedited access to specialist management.

CHAPTER FOUR: RESULTS

4.1 Social and demographic characteristics of study participants

The sample analysed consisted of a total number of 560 children seen at the paediatric outpatient department at The University Teaching Hospital in Lusaka, Zambia. The majority (77.8 %) were seen at the out- patient emergency room while 22.2 % were screened at the out -patient clinic. Over half (55.98%) of the children enrolled in this study were male and 44.1% were female. Majority of children (55.9%) sampled were aged above 60 months (5 years). Median age of participants was 68.5 months. Of the total children screened, caregivers of fifteen children stated that their child exhibited at least one of the red flag symptoms. These fifteen children were then subjected to the DSM V criterion, with eight children being identified as cases of ASD.

Most fathers of the autistic children were older than 30 years at the time of their child's birth, compared to fathers of the non-autistic children (87.5% and 34.4%, respectively). Most of the mothers of the autistic children were younger than 30 years old at the time of the child's birth compared to the mothers of the non-autistic children (25% and 81.7% respectively). The majority of fathers and mothers of the autistic children had a higher education status compared to the non- autistic group (87.5% vs. 17.4% and 75% vs. 10% respectively). Table 1 illustrates the social and demographic characteristics of the study participants and the comparisons between the autistic and non-autistic groups.

Table 1: Social and Demographic factors of the Study population

Characteristics	Non-Autistic n=552 (%)	Autistic n=8 (%)	P-Value
Gender			
• Male	305 (55.3)	8 (100)	0.011
• Female	247 (44.7)	0	
Age in Months	(Median= 69, SD =45)	(Median= 53, SD =27)	0.986
<36	150 (27.2)	0	
36-48	64 (11.6)	4 (50)	
49-60	51 (9.2)	1(12.5)	
>60	287 (52.0)	3(37.5)	
Maternal age at child's birth	451 (81.7)	2 (25)	0.000
• Less than 30 years	100 (18.1)	6 (75)	
• 30 years and above			
Paternal age at child's birth	360 (65.2)	1 (12.5)	0.002
• Less than 30 years	190 (34.4)	7 (87.5)	
• 30 years and above			
Paternal & maternal age > 30	23 (32.9)	6 (75)	0.002
Maternal education			
• Grade 12 and below	495 (89.7)	2 (25)	0.000
• Over grade 12	56 (10.1)	6 (75)	
Paternal education			
• Grade 12 years and below	455 (82.4)	1(12.5)	0.000
• Over grade 12	96 (17.4)	7(87.5)	

4.2 The clinical characteristics of children with red flags

Most of the children with red flags were male (12 out of 15) with the majority of them being aged above 60 months (8 out of 15). Five of these children presented with loss of language in the early developmental period. Ten children were unable to utter a single word by the age of 24 months. Of these, four children presented with inability to utter a single word both at 16 and 24 months respectively. Nine children with red flags had mothers older than 30 at the time of their birth, while 11 children had fathers aged 30 years and older at the time of their birth. Over half of the mothers had not completed twelfth grade, while most of the fathers (8 out of 15) had completed grade twelve and above.

Exposure to intrauterine alcohol and drugs was observed in about half of the children with red flags. Maternal exposure to alcohol was observed in six children, while only one mother had antenatal use of drugs other than the ones used in routine antenatal care (i.e. haematinics, anti- helminthic and anti-malarial drugs). Prematurity was seen in three of the children, while four children had birth weights less than 2.5kgs.

The fifteen children with red flags were then subjected to the DSM V criterion for ASD, with eight (53%) being identified as cases of ASD. All the cases of ASD were male with a median age at diagnosis of 52.5 months (4.3 years). Of the 8 children with ASD, 4 were aged between 36-48 months, while one was aged between 49-59 months and the rest were older than 60 months. One child had a previous diagnosis of ASD diagnosed at 38 months and was being followed up in a neurodevelopmental clinic. Six of the children with ASD presented with inability to utter a single word by the age of two years. This was the red flag most commonly observed in children with ASD. Two children with ASD presented with loss of previously acquired language skills in the early developmental period. This did not differ from that seen in the non- ASD group.

At the time of the child's birth, the parents of the children with ASD were older as compared to the non ASD group. Seven children had fathers with documented paternal age at child's birth above 30 years while 6 children had maternal age at delivery documented above 30 years. Parents of six children were aged older than 30 years at the

time of the child's birth. Majority of the Children (7 out of 8) had fathers with education level above the 12th grade.

Male sex, age between 36-48 month, inability to utter a single word by the age of two years, maternal and paternal age over 30 years and parents higher level of education were more common in children with a diagnosis of ASD within the group of children with red flags.

Table 2 illustrates and compares the clinical characteristics of the children with red flags (with and without ASD.)

Table 2: Characteristics of children with red flags

	CHILDREN WITH RED FLAGS N=15		
CHARACTERISTICS	**Children with red flags without ASD 7 (47%)**	**Children with red flags and ASD 8 (53%)**	**Total**
Gender			
• Male	4	8	12
• female	3	0	3
Age(months)			
• less than 36 months	1	0	1
• 36-48 months	0	4	4
• 49-60 months	1	1	2
• Above 60 months	5	3	8
Applicable Red Flag			
➢ Any infant who does not:			
• babble or coo by 12 months	0	0	0
• Gesture/grasp by 12 months	0	0	0
• Utter a single word by 16 months	1	3	4
• Utter two- word phrases(rather than repeating what has been said to him or her) by 24 months	4	6	10
➢ Any child who had any loss of language in early developmental age.	3	2	5
Maternal age at birth			
• Less than 30 years	4	6	6
• 30 years and above	3	2	9
Paternal age at birth			
• Less than 30 years	3	1	4
• 30 years and above	4	7	11
Paternal and maternal age above 30 years	0	6	6
Maternal education			
➢ 12 years and below	6	2	8

➢ Over 12 years	1	6	7
Paternal education			
• 12 years and below	6	1	7
• Over 12 years	1	7	8
Exposure to toxins			
• Alcohol	4	2	6
• Drugs	0	1	1
Gestational Age at birth less than 37 weeks	2	1	3
Birth weight below 2.5kgs	2	2	4
Maternal infection	2	1	3
Epilepsy	2	1	3

4.3 Reasons for referral of study participants and children with ASD

The participants of the study were seen at the hospital for various reasons. Nearly 20% of the screened children had respiratory complaints while those with epilepsy accounted for 12.4%. CNS complaints included headaches, febrile seizures and children referred for special needs assessment. Commonest complaints for children who were referred for special needs assessment included speech delay, hearing loss, slow learning and bizarre behaviour. Children who sought medical attention for other nonspecific complaints accounted for 24.1%

Eight of the children with red flags (53.3%) were referred for abnormalities in speech (6 for speech delay and 2 for incoherent speech). Three children (20%) were being followed up for epilepsy while four children were referred for ingestion of a poisonous substance, post exposure prophylaxis (PEP) for HIV, bizarre behaviour, and hyperactivity respectively.

Of the 8 autistic children, 2 (25%) were referred for speech delay and 3 (37.5%) for assessment for placement in a special school. Reasons for special school assessment included, slow learning at school, bizarre behaviour (aggression towards friends) and hyperactivity. The last three were referred for ingestion of a methyl spirit, post exposure prophylaxis (PEP) for HIV and poorly controlled seizures respectively. Figure 2 illustrates the reasons for referral or hospital visit for the children with ASD.
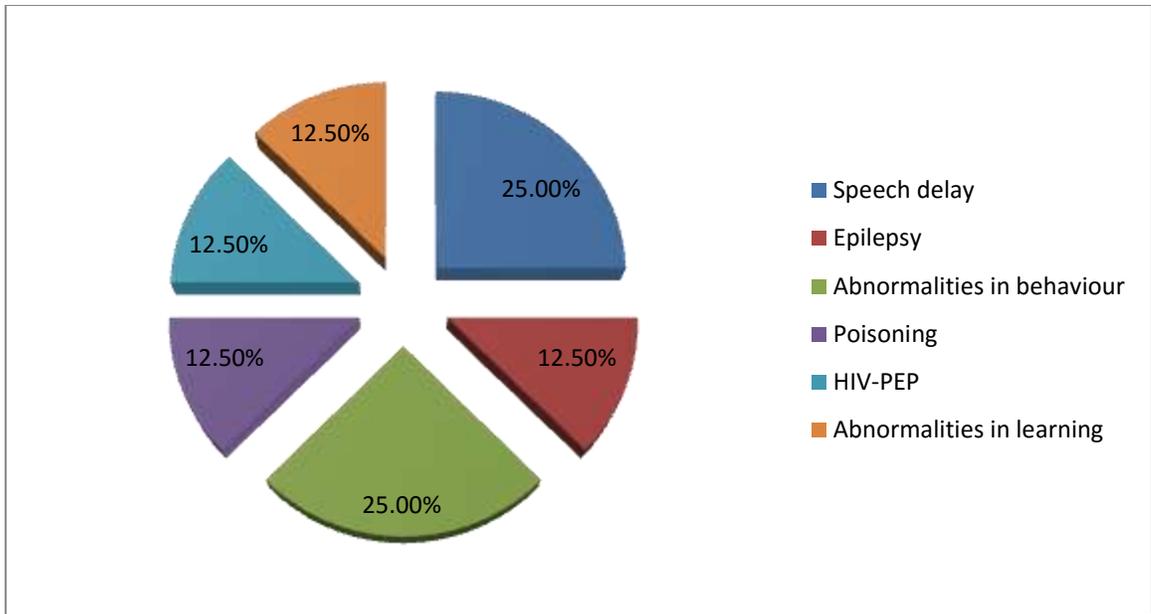
Figure 2: Reason for referral for children with ASD

4.4 Possible risk factors associated with ASD

Several factors have been postulated as possibly increasing the risk of developing ASD. In this study, six children with ASD (40%) had parents aged older than 30 years at the time of the child's birth. Maternal ingestion of alcohol during pregnancy and low birth weight were seen in 2 out of the 8 children (25 %) with the diagnosis of autism spectrum disorder respectively. Maternal infection and prematurity were seen in one child respectively. However no differences were found in exposure to toxins, prematurity, birth weight, maternal infections, epilepsy between non ASD and ASD children with red flags. (See table 2)

Figure 3 shows some possible associated risk factors for the children diagnosed with autism spectrum disorder as proposed in literature and as seen in this study.
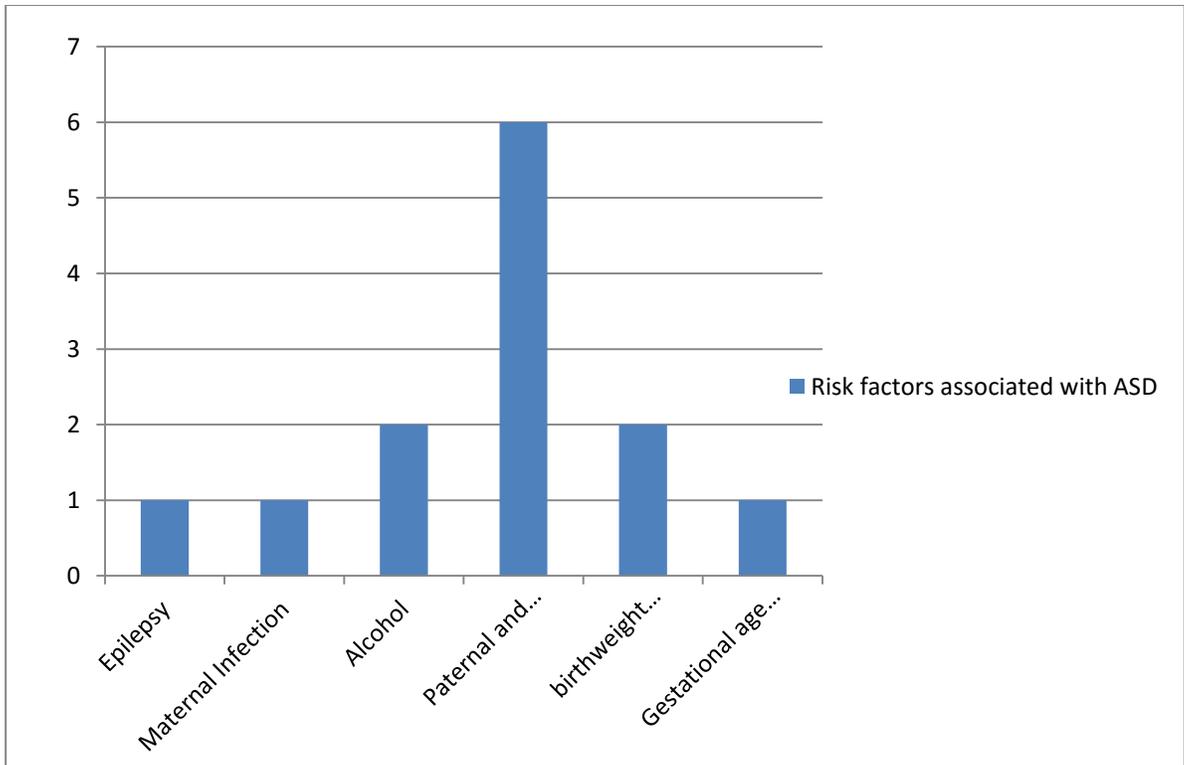
Figure 3: Risk factors possibly associated with Autism spectrum disorder

4.5 Clinical characteristic and severity level of the children ASD.

The case definition of ASD requires that there be deficits in social and communication domains across multiple contexts and the presence of repetitive patterns of behaviour either in the past or at the time of examination. There was heterogeneity in the presentation as is expected in the autism spectrum. Table 3 describes the clinical characteristics and behavioural patterns of the children diagnosed as having ASD based on parents/guardians report and one setting clinical observation. The majority (75%) of children (6 of the 8) were noted to have abnormalities in eye contact, failure of normal back and forth conversation and also elicited a history of having poor interest in the peers in their environment. Half of the children had echolalia and/ or the presence of idiosyncratic sounds being reported by the care givers.

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Table 3: Clinical characteristics and Behavioural patterns of the children with ASD (according to parents report and one setting clinical observation) based on DSM V criteria.*

A)Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following currently or in history	n=8(%)
Deficits in social emotional reciprocity	
• Abnormal social approach	4(50)
• Failure of normal back and forth conversation	6(75)
• Reduced sharing of interests, emotions or affect	3(37.5)
• Failure to initiate or respond to social interactions	3(37.5)
Deficits in non -verbal communicative behaviours used in interaction	
• Poorly integrated verbal and non-verbal communication	5(62.5)
• Abnormalities in eye contact and body language	6(75)
• Deficits in understanding and use of gestures	2(25)
• Total lack of facial expression	2(25)
Deficits in developing, maintaining and understanding relationships	
• Difficulties adjusting behaviour to suit various social context	3(37.5))
• Difficulties in sharing imaginative play or making friends	5(62.5)
• Absence of interest in peers.	6(75)

B)Restricted , repetitive patterns of behaviour, interests, or activities, as manifest by at least two of the following currently or in history

Stereotyped or repetitive motor movements, use of objects or speech	
• Simple motor stereotypes	0
• Lining up toys Or flipping objects	3(37.5)
• Echolalia/Idiosyncratic phrases	4(50)
Insistence on sameness, inflexible adherence in to routines or ritualized patterns of verbal or non -verbal behaviour	
• Extreme distress at small changes	4(50)
• Difficulties with transitions	2(25)
• Rigid thinking patterns and greeting rituals	1(25)
• Need to take same route or eat same food everyday	0
Highly restricted, fixated interests that are abnormal in intensity or focus	
• Strong attachment to or pre occupation with unusual objects	5(62.5)
• Excessively circumscribed or perseverative interests	5(62.5)
Hyper or hypo reactivity to sensory input or unusual interest in sensory aspects of the environment	
• Apparent indifference to pain/ temperature, Or textures, ,	1(12.5)
• adverse response to specific sounds	0
• excessive smelling or touching of objects	0
• visual fascination with lights or movement	0

***All the children fulfilled criteria C, D and E of the DSM V criteria for ASD (see appendix 1)**

Children with ASD present with varying levels of severity. The level of severity has an influence on the ultimate intensity of the intervention offered for each child. Severity levels for ASD are divided into 3 levels. According to the DSM V criteria for diagnosis of ASD, the level of severity is determined by the level of impairment of the behavioural symptomatology with levels one (1) and three (3) being the highest and lowest levels respectively. Levels 1, 2 and 3 correspond to individuals requiring support, requiring substantial support and requiring very substantial support respectively. These severity levels are dependent on the severity of the social communication impairment and restricted, repetitive behaviours symptomatology. Half of the children (4 out of 8) in this study were assessed as severity level 2, while 3 children as severity level 1 and only one child as severity level 3. Table 4 illustrates the assessed severity levels of the children diagnosed with autism spectrum disorder in this study.

Table 4: Severity level and behavioural characteristics of ASD cases*

CASE N=8	Age (months)	A (3/3)	B (2/4)	SEVERITY LEVEL
1	44	3	2	2
2	57	3	3	1
3	96	3	3	3
4	108	3	3	2
5	48	3	2	2
6	48	3	3	1
7	48	3	3	2
8	96	3	3	1

*all the participants fulfilled the sub-categories C, D, E of the DSM V criteria. Diagnosis of ASD requires that all three sub categories of part A and at least two out of four sub categories of part B of the DSM V in addition to C, D, and E be present. This is the case definition of ASD according to the DSM V criteria.

A -Persistent deficits in social communication and social interaction across multiple contexts
B- Restricted, repetitive patterns of behaviour, interests, or activities.

CHAPTER FIVE: DISCUSSION

5.1 Social and Demographic characteristics of children with ASD

Social and demographic factors may influence recognition, diagnosis and management of ASD *(Russel et al, 2011)*. Social stigma surrounding the behavioural manifestations of ASD may have a negative impact on the affected families and the community understanding of ASD. It may introduce a sense of social awkwardness and later affect the social relationships of these families. Other factors like demographic distribution may also play a role in the timely diagnosis and management of ASD. While families in the urban areas may have easy access to health facilities, this may not be the situation with families in the rural areas of the country who have to travel long distances to access medical care. This leads to delay in the diagnosis of ASD. A higher parental age and higher parental education has been associated with earlier diagnosis of ASD (*Hrdlicka et al, 2016)*. In this study, the paternal and maternal education level of the children with ASD was relatively high (six mothers (75%) and seven fathers (87.7%). This was higher than that found in a South African, retrospective study which highlighted that up to 60.3 % of mothers had an education level higher than the tenth grade (*Springer et al, 2010*). These high parental education levels may have had an influence on seeking early medical assessment for their children.

5.2 Possible associated risk factors for ASD

The aetiology of ASD is complex and heterogeneous, with both heritable and non-heritable factors being at play. Studies relating advanced parental age at the time of the child's birth have had mixed conclusions *(Hultman et al, 2010).* In this study, seventy five per cent of children diagnosed with ASD had mothers older than 30 years at the time of their birth with only one child with paternal age above 40 years. Both parents were older than 30 years in 75% of children with ASD at the time of the child's birth. This is in keeping with a study done by Shelton *et al* in the United States of America that demonstrated that an increase in parental age, particularly advancing maternal age increased the risk of bearing a child with ASD regardless of the age of the father. Shelton *et al* In the same study showed that the risk of autism was associated with advancing paternal age primarily among mothers aged below 30 years and that it had

little effect when mother was above 30 years. This was not seen in this study. Our sample size was too small for us to draw any conclusion.

Other recognized risk factors associated with a high risk of developing ASD include maternal viral infections, particularly rubella *(Piven et al, 1993)* and maternal drug use in the period of early brain development. Maternal infection (fever during pregnancy) was present in only one mother. Mothers of 2 (25%) children with ASD reported having taken minimal (not better specified) amounts of alcohol during pregnancy. Although pre natal alcohol exposure has been shown to have an association with autism (*Pickler et al, 2009)*, a Danish study examined the association between moderate to light pre natal alcohol exposure and development of ASD in the off spring in a population based study involving 80 552 children and their mothers and concluded that there was no significant association between the two (*Elliasen et al,2010*). Two series of case reports have indicated a high prevalence of ASD among children with fetal alcohol syndrome in mothers with excessive drinking patterns in pregnancy (*Harris et al 1995, Nanson et al, 1992*). One mother with maternal pre-eclampsia reported the use of anti-hypertensive drugs in pregnancy. These individual non heritable risk factors have not been shown to be exclusive independent risk factors in the development of ASD. More studies are needed to support any one risk factor as being exclusively associated with ASD.

No single obstetric factor is a likely cause of autism but underlying genetic factors and their interaction with the environment would likely explain the increase in the prevalence of autistic disorders *(Glasson et al, 2004)*. In the past , preterm delivery was thought to be a cause of ASD. More recently, studies have implicated maternal and pre natal complications/morbidities among preterm births, low birth weight and being small for gestational age as primarily increasing the risk of autism spectrum disorders in preterm births (*Buchmayer et al, 2009*, *Gardener et al, 2011*). Low birth weight is seen in 23.1 % of all babies born in Zambia (*Kasonka et al, 1998*). Two of the 8 children (25%) with autism had low birth weight (less than 2.5kgs) at the time of their delivery. This is higher than 13.8% found in a South African study by Springer et al (8 of 58 children), but likely not a significant finding in this study population. Only 1 (12.5%) autistic child had a preterm delivery (less than 37 weeks) in this study.). There was no

demonstrable difference in gestational age at birth, low birth weight, maternal infection between the ASD and non- ASD children with red flags.

None of the children with autism in this study had siblings or first or second degree relative with ASD. Often families are unwilling to reveal certain neurological pathologies in the families due to possible stigma and relational implication to the family.

5.3 Screening with the Red flags of Autism

The red flag symptom check list used was based on a self-reporting system. The red flags are simple, early warning signs that can be used to screen for children at risk of autism and other developmental disabilities. The association between late babbling and language impairment has been observed in ASD (*McCleery et al, 2006)* and language impairments can be seen as early as 14 months in the majority of children diagnosed with ASD at the age of 24 months(*Landa et al, 2006).* In this study the red flag symptom check-list used had a positive predictive value (PPV) of 53%.With a PPV of 53%, another more specific tool is needed to make a diagnosis of ASD. The red flags cannot substitute the need of using more specific diagnostic tools for diagnosing ASD. The simplicity and ease of use of these red flag symptoms does however make them a quick and simple way for health providers at all levels to screen for ASD. This ultimately promotes early referral of children with red flags to institutions capable of performing a thorough diagnostic assessment. These may also be useful at very busy primary health centres and rural health centres around the country. The commonest characteristics observed in children with ASD within the red flag group were, male sex, age between 36-48 month, inability to utter a single word by the age of two years (non-verbal symptom), maternal and paternal age over 30 years and a high parental education level.

5.4 Prevalence of ASD

There has been a worldwide increase of ASD. This increase cannot be extrapolated to the African context as very few epidemiological studies have been done in sub Saharan Africa. There is a critical shortage of research in the field of autism in sub Saharan

Africa. This may have an impact on the low levels of awareness and late identification of children living with ASD. Hospital prevalence of ASD differs from general population prevalence. Hospital prevalence is expected to be higher than general population prevalence.

It is important to note that the prevalence of ASD (1,47%) found in the United States of America was a population based study done in children aged 8 years old. In view of the difference in methodology, the prevalence found in this study cannot be directly compared to the prevalence found in USA. With this study being hospital based, it can be speculated that prevalence of ASD in the Zambian general population might be lower than that found in the USA. More studies are needed to verify this speculation. The relatively high prevalence in this study could be explained by the fact that this study was done at a tertiary hospital where a number of children with different neurodevelopmental conditions are referred for further assessment and management. Some children are still missed as they are sent to psychiatric departments/ hospitals around the country and are possibly misdiagnosed. Early identification and management of children with ASD still remains a challenge at this tertiary institution as some patients with ASD still go unrecognized or misdiagnosed. The lack of proper screening tools and training of health practitioners at all levels may account for some of the missed cases. The prevalence of ASD has been shown to be higher in males than in females by at least three to four times in other studies (*Bakare et al, 2011*), this was a consistent finding in this study as all the diagnosed children were male. With the diagnosis of ASD being made between the age of two and six years, the median age of diagnosis in this study was 52.5 months(4.3 years).This is higher than that found in a South African study where the mean age of diagnosis was 42 months (3.5 years) (*Springer el, 2010*). This late detection of children with ASD warrants an increase in awareness programs in the communities as early diagnosis and intervention is fundamental in the management of ASD. As the increasing prevalence of ASD may be considered a public health concern, there are calls for more funding and research directed towards studies that determine factors associated with the observed late diagnosis of ASD in Africa (*Bello-Mojeed et al, 2014*).

5.5 Clinical characteristics and behavioural patterns of children with ASD

Children with ASD manifest with deficits in both expressive and receptive language .These language impairments may range from deficits of expressive language to use of idiosyncratic language, echolalia and abnormalities in intonation and volume control. *(Mody and Belliveau, 2013)*. Childhood apraxia of speech is common in children with ASD but may be absent in children with verbal ASD (*Shriberg et al, 2013*). In Africa, a surplus of non-verbal (lack of expressive speech) cases of ASD have been reported *(Bakare et al, 2011, Belhaj et al, 2006).* This might be because non-verbal children with ASD are easily recognised and often families seek early medical attention. Springer et al did however note a minority of children with regression of previously acquired speech attending a Western Cape hospital.

As ASD is a spectrum, the symptomatology observed in this study was diverse. Over half (62.5%) of the children (5 of 8) presented with speech delay/ poorly integrated verbal communication. This is lower than that found in Saudi Arabia *(Al-Zahrani, 2013)* and India (*Kondekar et al, 2016)* (80 and 83.03% respectively). Children with milder symptoms may have some speech, though it may not always be fluent and their intent for comprehensible communication may be absent. There are disparities in the percentages of verbal abilities of children with ASD among African studies (*Springer et al, 2011, Bello –Mojeed,2017).* This may be due to the differences in methodology of diagnosis and assessment of language functions. Two of the children with ASD (25%) presented with regression of previously acquired language skills. This is a little higher than observed in an Indian study that demonstrated that 18 % of the autistic children had regression of previously acquired language skills without regression of other motor milestones (*Kondekar et al, 2016*).It has been shown that up to 25 to 30 % of children with ASD begin to say words and then stop speaking usually between the ages of 15-24 months (*Turner et al, 2006*). Failure of normal back and forth conversation, abnormalities of eye contact and body language and absence of interest in peers were the predominant features of ASD seen in this study. As this is the core symptom of ASD, this was not a surprising finding as it has been replicated worldwide. Fifty per cent of children with ASD presented with echolalia and use of idiosyncratic phrases. Echolalia was present in all the children with ASD with severity level 1.

Over half of the children (62.5%) presented with strong attachment to or pre-occupation with unusual objects and this accounted for the major presentation of repetitive and restricted patterns of behaviours. This is a little higher than that observed in an Indian study in which 50% of children presented with stereotypical movements (*kondekar et al, 2016).*

The described clinical and behavioural characteristics were based on parental reports and a single clinic observation. The absence of the other functional impairments in some of the children cannot be totally excluded as several evaluations at different times and settings may have yielded additional results. The evaluation of these children by other more experienced personnel who play a vital role in the management of children with ASD would have been an added advantage in assessment of these children.

5.6 Co morbid conditions associated with Autism spectrum disorder

.The presence of epilepsy has been shown to worsen the prognosis, morbidity and mortality of children with ASD *(Mauridsen et al, 2008).* Epilepsy has been shown to occur in about 5-40% of children with ASD (*Matson et al, 2009*). In this study only 1 child (12.5%) with ASD was being followed up for epilepsy. This is similar to that observed in a South African study of 10.3% (6 of 58 children) *(Springer et al, 2011).* The child with epilepsy had epilepsy of unknown aetiology with generalised tonic-clonic seizures and an ASD severity level of 3 which required substantial support to facilitate his daily living. None of the children in this study had severe sleep dysfunction. Of the 8 children with ASD, two (25%) had hyperactive behaviour but did not qualify as having ADHD according to the DSM V criteria. Hyperactivity, inattention and impulsivity are common symptoms in children with ASD. These are the core features of ADHD and this may lead to an overlap of diagnosis.

 Children with ASD will in addition to the above symptoms have marked deficits in communication skills and the added presence of stereotypic repetitive patterns of behaviour. The presence of hyperactivity and inattention have been shown to exaggerate the severity of ASD, hence children with both diagnosis are more functionally impaired than those with a separate diagnosis *(Sprenger et al, 2013).* This distinction is important because children with ASD/ADHD require a different approach in their management.

Several neurological conditions have been shown to occur co-morbidly with ASD. Recently, motor impairment, epilepsy, and sleep dysfunction are among the neurological co-morbidities that are being actively researched. In addition to the core symptoms of ASD, these conditions markedly affect function and outcome of intervention offered to children with ASD. Therefore, routine screening for neurological conditions that could co-morbidly occur with ASD should be done as part of diagnostic assessment and management in individuals with ASD.

CHAPTER SIX: CONCLUSION AND RECOMENDATIONS

6.1 Conclusion

The prevalence of ASD at this tertiary institution was 1.4%. Parental age above 30 years at the time of the child's birth and high parental education levels were the most commonly observed socio-demographic characteristics in the group of children with ASD. The more commonly observed clinical characteristics of children with ASD within the red flag group included, male sex, age between 36-48 months, inability to utter a single word by the age of two years (non-verbal symptomatology). The red flags of autism are an easy and quick way of screening for ASD; however, they should not substitute the use of a more specific diagnostic tool for ASD. There is an urgent need to increase public awareness and knowledge of the early warning signs of autism in order to promote early diagnosis of ASD. Health personnel at all levels should be trained in the recognition, diagnosis and management of children living with ASD. More centres are needed countrywide to address the needs of children with neuro-developmental disorders particularly ASD. Large scale population studies are needed to ascertain the prevalence of ASD at national level.

6.2 Limitations

The study had several limitations:

1. A single clinical assessment may have omitted certain impairments in the children that participated in this study. Ideally children with ASD should be evaluated in more than one context and occasion. Assessment of these children by another independent physician would have been prudent to exclude interviewer bias.

2. Assessment by a multi-disciplinary team may have helped to better understand the level of functional impairment in the children diagnosed with ASD.

3. Performance of a cognitive assessment may have been useful to complete the evaluation of these children. Cognitive dysfunction is varied among individuals with ASD and may be pivotal in the intervention strategies applied in each child. However, this may be difficult to perform in children with ASD.

4. The Developmental intervention clinic (a neurodevelopmental clinic) at the University Teaching Hospital was excluded from this study as it is known that the prevalence of ASD in children with special needs is higher than that found in the general population. Therefore, other children may have been missed as they were referred directly to the Developmental interventional clinic and may not have passed through the areas were sampling was taking place.

5. As this is not a population based study, it cannot be used as a proxy for national prevalence of ASD in Zambia. Larger studies are needed in schools, hospitals and communities across the country for this estimation to be possible.

6. Some social demographic information was not collected, like housing, parents' income and rural/urban areas, hence the effect social economic status on diagnosis of ASD could not be adequately elicited.

6.3 Recommendations

1. More awareness about ASD is needed in the communities and in schools. This will encourage the parents with low education and social-economic background to bring children with early warning symptoms for assessment.

2. There is an urgent need for more health practitioner's to be trained in diagnosis and management of children with ASD. There is need for more speech, behavioural and cognitive therapist's country wide as these form the core of multi-disciplinary management of children with ASD as development of language and communicative strategies is an important focus.

3. Screening for ASD and other neuro-developmental disorders in Zambia should be become routine for well -baby visits at 12, 18 and 24 months as recommended by the American academy of Pediatrics. This promotes early detection and ultimately early intervention

4. There is need for more developmental intervention centres country wide so as to offer early and timely management of children with neuro-developmental conditions. Currently Zambia has got one developmental intervention clinic

located at the University Teaching Hospital. Affected parents and children have to travel long distances to access this facility.

5. Despite the fact that children with ASD have different levels of severity, commonly they are all placed in special schools have do not adequately cater for their needs. There is need for more schools that will particularly manage children with ASD.

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APPENDIX 1: DSM V CRITERIA FOR DIAGNOSIS OF ASD (2013)

A.   Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history

1.   Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

2.   Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

3.   Deficits in developing, maintaining, and understand relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peer

Severity is based on social communication impairments and restricted, repetitive patterns of behaviour.

B.   Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history

1.   Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2.   Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

3.   Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4.   Hyper- or hypo reactivity to sensory input or unusual interest in sensory aspects of the environment (e.g. apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement)

Severity is based on social communication impairments and restricted, repetitive patterns of behaviour.

C.   Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D.   Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E.   These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level

Severity is based on social communication impairments and restricted, repetitive patterns of behaviour

Severity level	Social communication	Restricted, repetitive behaviours
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches	Inflexibility of behaviour, extreme difficulty coping with change, or other restricted/repetitive behaviours markedly interferes with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and how has markedly odd nonverbal communication.	Inflexibility of behaviour, difficulties coping with change or other restricted/repetitive behaviours appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.

| Level 1 " Requiring support" | Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful response to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to- and-fro conversation with others fails, and whose Inflexibility of behaviour causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence. Attempts to make friends are odd and typically unsuccessful. | Inflexibility of behaviour causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence. |

APPENDIX 2: INFORMATION SHEET

The prevalence and clinical characteristics of Autism spectrum disorder in children aged 1-15 years seen at the University Teaching Hospital in Lusaka, Zambia

Dear parent/ guardian,

Introduction

You and your **child** are invited to take part in this study**. Autism spectrum disorder is condition that affects how children interact and, communicate with other people. It also leads to behavioural challenges**. It has been noted that the burden of Autism spectrum disorder at the University teaching hospital is not known. And to help us establish the prevalence we require your support.

There has been an increase in the occurrence of autism spectrum disorder in other parts of the world and we would like to know if the same is true at our hospital.

Study title

The prevalence and clinical characteristics of Autism spectrum disorder in children aged 1-15 years seen at the University Teaching Hospital in Lusaka, Zambia

Principal investigator

Dr Kafula Lisa Nkole, a post graduate student doing specialist training in the department of Paediatric and child health at the University of Zambia, School of medicine.

Purpose of the Study

The purpose of the study is to determine the burden of Autism spectrum disorder at the University Teaching Hospital in Lusaka, Zambia. This will help pick up patients early and therefore early intervention can be instituted to help provide a better quality of life.

Study procedure

Parents or guardians with children that meet the criteria for enrolment will be asked to sign a consent form agreeing to take part in the study after any questions or clarifications they may have, have been answered. There are certain behaviours (red flags) that may raise the suspicion of Autism spectrum disorders. If your child has these behaviours, we will ask you a few questions from a questionnaire for about 10 minutes.

You may be asked to come back on another day so that your child can be further examined by interaction with the investigator (myself) to observe if he/she meets the criteria for the diagnosis of Autism spectrum disorder. We shall refund your transport costs for this reason.

There are no monetary incentives for participating in this study. Participation in this study is voluntary. Any decision made not to participate in the study will not affect the medical care of your child. If you do decide to take part, you are free to skip any questions you may deem personal and withdraw from the study at any point without any consequences. This will not affect the medical care of your child. You will not be required to provide any reason for your decision to withdraw.

Risks and benefits

It is our belief that the procedure for this study will not harm the patient in anyway. However we will take up a bit of your time (30-45 minutes) for us to assess your child fully.

Early detection and early intervention plays a big role in taking care of children with Autism spectrum disorders. If your child is found to have Autism spectrum disorders, we will refer you to the developmental intervention clinic (DIC) for the management and follow up they require.

Confidentiality

Personal information will be kept private at all times. The child's medical record will be treated just as any other hospital medical records. Each participant will be assigned a code number for the purposes of identification. All information collected will be stored in a lockable cabinet located in a secure environment with restricted access to two research assistants and the principal investigator-myself. Information from this study may be used for other research purposes and may be published however names of participants will not be made public.

Contact details

Should you need further information, clarifications or concerns regarding your participation in this study please use the details provided below to contact either the principal investigator (myself) or the secretary to the ERES CONVERGE BOARD.

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The prevalence and clinical characteristics of Autism spectrum disorder in children aged 1-15 years seen at the University Teaching Hospital in Lusaka, Zambia

Participant's guardian/parent

I_____ (participant's parent or guardian's name, signature or thumb-print) hereby confirm that this study has been explained to me. I hereby voluntarily give consent for my child and i to participate in this study.

Signature/Thumb: _____   Date: _____

Witness name:_____

Signature: _____

Date: _____

Interviewer

I have explained this research study to the participant's guardian/parent and I am prepared to answer all queries that may arise both now or in the future regarding the study and the participant's rights. I have explained that participants may withdraw from the study at any given time without any consequences.

Investigators name: _____

Signature: _____

Date: _____

Witness name:_____

Signature: _____   Date: _____

APPENDIX 4: ASSENT FORM FOR CHILDREN AGED 7-15 YEARS.

The prevalence and clinical characteristics of Autism spectrum disorder in children aged 1-15 years seen at the University Teaching Hospital in Lusaka, Zambia

Interviewer

Having explained the steps of the study to you and your parents/guardians, I am inviting you to participate in our study. I am available to answer any questions that you may have now or in the future concerning the study and your participation in this study.

Investigators name: _____

Signature/ thumb print: _____

Date: _____

Witness name:_____

Signature/thumb print: _____

Date: _____

Participant

I ……………………………….. (Participants name) in the presence of my parents/guardian and with their consent, do agree voluntarily to participate in this study.

Participant's name: _____

Signature/thumb print: _____

Date: _____

APPENDIX 5: DATA COLLECTION SHEET

The prevalence and clinical characteristics of Autism spectrum disorder in children aged 1-15 years seen at the University Teaching Hospital in Lusaka, Zambia

Patients study number: _____

Reason for referral: _____

Red Flag symptoms   1) Yes   2) No

Patients Demographics:

Age: _____

Sex: 1) male   2) Female

Ethnicity: 1) black   2) white   3) Indian   4) mixed race   5) other

Parent's demographics:

Age: _____

Maternal age at birth: _____

Paternal age at birth: _____

Education

Maternal education: _____

Paternal education: _____

Past medical history:

Co-morbid conditions: 1) Yes   2) No   if yes, specify_____

Developmental history:

Social smile: _____   Walking: _____

Sitting: _____   Talking: _____

Standing: _____

Antenatal history:

Toxin exposure: 1) Alcohol   2) Other

Maternal infection: 1) Yes (fever, rash, cold/ flu symptoms)   2) No

Maternal medication:1) Anti-convulsants 2) other

Birth history:

Gestational age at birth: _____

Birth weight: _____

Asphyxia: 1) Yes   2) No

Head circumference at birth:

Family history:

Sibling with ASD: 1) Yes   2) No

Learning disabilities: 1) Yes   2) No

Consanguinity: 1) Yes   2) No

CLINICAL FINDINGS

Weight: _____   Head circumference: _____

Height: _____

Neurological Exam:

PARAMETER	NORMAL	ABNORMAL	IF ABNORMAL, SPECIFY
General appearance (i.e. dysmorphic features, pallor, jaundice)			
Mental status			
Vision			
Hearing			

Gross motor			
Fine motor			
Reflexes			
Co-ordination			
Station and gait			
Cranial nerves			

Proceed to DSM 5