SICKLE CELL DISEASE ASSOCIATED CO-MORBIDITY WITH PNEUMONIA OUTCOMES AMONG UNDER-FIVE CHILDREN REFERRED TO UNIVERSITY TEACHING HOSPITAL BETWEEN 2011- 2013 IN LUSAKA, ZAMBIA

By

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A thesis submitted to the University of Zambia in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology.

The University of Zambia

Lusaka

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DECLARATION

I **Muchanga Muzala.S** do hereby declare that this is my own work and all the sources of materials and publications used herein have been acknowledged. This document presented for the Master of Science in Epidemiology Degree has not been previously submitted either wholly or in part for other Degree at this or any other universities.

Signed: ……. Date: ……

Muchanga Muzala.S

APPROVAL

This dissertation by Muchanga Muzala.S is approved in partial fulfilment of the requirements for the award of Master of Science in Epidemiology by the University of Zambia.

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DEDICATION

I dedicate this research work to my late grandparents Mary and Able Mwanashimbala, family members, friends and the Public Health team at University of Zambia who have been encouraging me throughout the whole period of my study

I dedicate also to my wife, Naomi Muchanga and children, Ethaniel, Shekinah, Jethroreuel and Gianuriel Muchanga for understanding me during the school programmes

I give praise to my God for helping me through hard times.

ABSTRACT

Pneumonia in sickle cell disease (SCD) can be particularly severe and has come to be called acute chest syndrome (ACS). ACS is a frequent complication of sickle cell disease in patients hospitalized with vaso-occlusive crisis (VOC). It is associated with a high risk of sickle cell-related mortality and morbidity in children, including prolonged hospitalization. The aims of this study were to determine the prevalence of pneumonia in sickle cell disease, and also to determine cells that are mostly associated with pneumonia in sickle cell disease. Furthermore, were to determine outcomes of pneumonia in SCD and pneumonia for under-five children referred to University Teaching Hospital.

The study employed a cross-sectional design, using secondary dataset from paediatrics wing within University Teaching Hospital. Complete enumeration was applied.
Continuous data were summarised by means and standard deviation while frequencies and percentages were used for categorical data. The data was analysed using STATA version 13.0 (Stata Corporation, College Station, TX). Logistic regression was applied to assess associations of study variables.
A total of 601 under-five children with pneumonia was studied for their pneumonia in SCD. Out of 601 under-five children, 84 had pneumonia in SCD, while 517 had pneumonia only. The under-five children comprised of 53% (n=317) males and 47% (n=284) females, their ages ranged from 28 days to 59 months years old, with a mean age (±SD) of 2.8 ± 1.4 months years old. The prevalence of pneumonia in sickle cell disease was 14%. Mortality for pneumonia in SCD was 12.8% (n=15) while in pneumonia only was 87.2% (n=102). Furthermore we established haemoglobin, red blood cells, white blood cells, mean cell haemoglobin and monocytes as cells that are mostly associated with pneumonia in SCD.

The study achieved its set objectives, by determining pneumonia in SCD prevalence, haematological parameters which are mostly associated with pneumonia in SCD, and the outcomes of pneumonia in SCD. Therefore, the government through the Ministry of Health and other partners need to formulate policies towards the reduction of pneumonia in sickle cell disease burden in Zambia.

Key terms: Sickle Cell Disease (SCD), Co-Morbidity, Pneumonia Outcomes

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ACRONYMS

AA	Genotype Normal of sickle
ACS	Acute chest syndrome
VOC	Vaso-occlusive crisis
AS	Genotype carrier of sickle cell
BT	Blood transfusion
ARDS	Acute respiratory distress syndrome
GAG	Guanine Adenine Guanine
GTG	Guanine Thymine Guanine
Hb	Haemoglobin
HbA	Normal Haemoglobin
HbF	Fetal Haemoglobin
HbSS	Sickle cell Haemoglobin
HU	Hydroxyurea
ZCAHRD	Zambia centre for applied health research development
MCHC	Mean cell haemoglobin concentration
RBC	Red blood cells
SCA	Sickle cell anaemia
SCD	Sickle Cell Disease
SS	Sickle cell
UNZABREC	University of Zambia-Biomedical research ethics committee
UTH	University Teaching Hospital
WHO	World Health Organization
CHCM	Comprehensive health care management
PERCH	Pneumonia etiology research for child health

CHAPTER 1

INTRODUCTION

1.1 Background

Pneumonia in patients with sickle cell disease (SCD) can be particularly severe and has come to be called acute chest syndrome (ACS). ACS is a frequent complication of sickle cell disease in patients hospitalized with vaso-occlusive crisis (VOC). It is associated with a high risk of sickle cell-related mortality and morbidity in children, including prolonged hospitalization. More than half of all children with homozygous SCD (HbSS) experience at least one episode of ACS in the first decade of life (Gill et al., 1995). Recurrent episodes may herald the onset of debilitating chronic lung disease (Powars et al., 1988). Although most of the evidence for clinical management and prevention is derived from the experience in patients with HbSS, ACS should be aggressively managed irrespective of the SCD genotype (Shilpa et al., 2017).

Individuals with SCD are reported to be susceptible to infections with encapsulated organisms such as *Streptococcus pneumoniae*. Aside from the fact that the data regarding the clinical spectrum of SCD are limited, there was controversy regarding the role and significance of pneumococcal disease in causing morbidity and mortality in SCD. However, there is emerging evidence to confirm that pneumococcal disease is a significant cause of bacteraemia in SCD, with calls to introduce interventions for preventing infections as a critical factor in improving survival (Makani et al., 2013). The various factors that are associated with increased infections in SCD may be directly related or unrelated to the immune system. SCD causes end-organ damage to the lung, liver, kidney, and skin, making these sites susceptible to infection by unusual organisms (Makani et al., 2013).

Acute chest syndrome reflects the difficulty in distinguishing pulmonary infection (viral or bacterial pneumonia) from other conditions that may occur in SCD, including inflammatory changes following pulmonary fat embolism or pulmonary infarction by microvascular occlusion or thromboembolism. Bacterial infection is diagnosed by culture of a respiratory pathogen from sputum or blood, but such cultures are negative in the majority of ACS cases. Consequently, the historical term ACS cannot be discarded until better diagnostic testing becomes available (Maitre et al., 2000).

Acute chest syndrome clinically and radiologically resembles bacterial pneumonia. However, the clinical course of ACS in persons with sickle hemoglobinopathies is considerably different from that of pneumonia in hematologically normal individuals. Multiple lobe involvement and recurrent infiltrates are more common in SCD, and the duration of clinical illness and of radiologic clearing of infiltrates may be prolonged to 10 days or longer. Acute pulmonary infiltrates are particularly difficult to classify in sickle cell disorders because of the potential for rapid progression from mild hypoxia to pulmonary failure, acute respiratory distress syndrome (ARDS), and multiorgan failure as a consequence of disseminated microvascular occlusion. Any decline in arterial oxygen saturation increases the fraction of polymerized Hb S with a subsequent deleterious effect on blood flow and pulmonary function (Vichinsky et al., 1997). ACS is associated with considerable morbidity and both acute and delayed mortality. The incidence is highest in children 2 to 4 years of age and, while gradually declining with age, remains common in adults (Nansseu et al., 2015).

1.2 Statement of the Problem

Children with sickle cell disease (SCD) often have functional asplenia, with dysfunctional antibody production and poor opsonophagocytosis, making them susceptible to encapsulated bacteria, especially *Streptococcus pneumoniae* (Beauvais et al., 1982, Battersby et al., 2010). Children with SCD have a 600-fold higher risk of pneumococcal disease compared with their healthy peers (Overturf et al., 1977). Children with SCD remain at increased risk of pneumonia in spite of all the current interventions, including newborn screening, early referral for long-term specialist care, recommendations for daily penicillin prophylaxis from 3 months of age and timely immunisation with high uptake rates (Oligbu et al., 2017). Pneumococcal disease approximately affects 10% of children with SCD by age 5 years, (Powars et al., 1975) an infection risk that is 300 times greater than that in the general population (Barrett-Connor et al., 1971). This susceptibility is primarily attributable to functional asplenia (Pearson et al., 1969).

Sickle cell disease is one of the neglected diseases known to be occurring in Africa. More than 75% of the global burden of SCD occurs in sub-Saharan Africa where scarce health resources and inadequate awareness among health care providers and the general public contribute to high rates of early mortality. With few data from neonatal screening programs, and virtually no prospective natural history studies, true mortality rates, and pneumonia cases are unknown. An estimated 50% to 90% of infants born with SCD in sub-Saharan Africa die .

before their fifth birthday, due either to complications of sickle cell itself or more commonly from pneumococcal disease, malaria, or diarrheal disease (Grosse et al., 2011). Naturally, SCD is associated with other co-morbidities. However, the exact burden associated with sickle cell and pneumonia is unknown. Pneumonia in SCD has now become a global health problem due to large number of people who are affected by the disease worldwide (Scott at el., 2011). Infections are the most common cause of death among Zambian sickle cell disease children. A study by Athale et al observed that infections accounted for 29.84% of mortality among sickle cell patients (Athale et al., 1994).

In Zambia, according to the Pneumonia Aetiology for Child Health (PERCH) study, there were a total of 14 923 inpatient paediatric admissions to the University Teaching Hospital in Lusaka in 2008, of these admissions, 3467 (23%) were for acute respiratory illness. Over a thousand of the cases (30%) occurred in children, five years of age. The case fatality rate of severe pneumonia was 25.8% (Orin et al., 2012). In many parts of sub-Saharan Africa, SCD is responsible for up to 6% of all child deaths (Orin et al., 2012). This situation calls for concern as it may derail the recent improvements in overall child survival which is at the heart of the health care systems.

Despite infections being a common cause of morbidity and mortality, no studies have been done to know the prevalence of pneumonia in SCD and the association of pneumonia and SCD. As such sickle cell disease patients presenting with fever are usually treated blindly with a combination of benzyl penicillin and chloramphenicol as first line treatment.

This treatment policy may delay appropriate treatment of the patients in cases where the prevailing organisms are not targeted since they are unknown, this may increase the cost of treatment of these patients. It is, therefore, important to identify the prevalence of the pneumonia in SCD and its association.

1.3 Rationale of the study

Acute chest syndrome (ACS) is a leading cause of hospitalization in sickle cell disease (SCD) and is currently the main cause of death in children with SCD in both well-resourced countries and not well-resourced countries (Hamideh et al., 2013). Recurrent episodes of ACS can negatively impact lung function in the long term (Sylvester et al., 2006). The burden of sickle-cell disease in the African Region is increasing with the increase in population. This

has major public health and socioeconomic implications. ACS in individuals with sickle-cell is uncommon but may occur under certain circumstances. Clinical deterioration and death are potential outcomes, and a delay in diagnosis may worsen the rates of morbidity and, most likely, of mortality.

The study provides knowledge of prevalence for pneumonia in SCD, which is important in determining the morbidity and mortality of the pneumonia in SCD. However, currently little is known about the prevalence for pneumonia in SCD. We also determined the Haematological profiles which are mostly associated with pneumonia in SCD and further compared mortality for pneumonia in SCD and pneumonia. The study determined the possible association between pneumonia and sickle cell disease among under-five children referred to University Teaching Hospital. However, there is limited documentation in the literature on the possible association between pneumonia and SCD.

The study provides important information or results to the scientific, public health and policy communities that influence treatment algorithms and diagnostic approaches in order to reduce the morbidity and mortality of the pneumonia in SCD.

This study provides further evidence of the fact that public health problems represent global issues that need to be addressed collectively by low-income and high-income countries. The likelihood of finding co-morbidity and genetic disorders that previously had a restricted distribution has increased in recent decades, and this trend is unlikely to change in the near future. Countries can adopt national measures, such as screening programmes for pneumonia in sickle cell disease in order to reduce the local national and global burden of such disorders and co-morbidity, but in the long term, a concerted approach based on multinational collaborations and partnerships focusing on countries of high prevalence would probably be much more effective; this approach is particularly relevant for co-morbidity.

1.4 Research Question

What is the association between sickle cell disease and Pneumonia outcomes among under-five children referred to the University Teaching Hospital (2011- 2013) in Lusaka Zambia?

1.5 General Objective

To determine the sickle cell disease associated co-morbidity with pneumonia outcomes among under five referred to university teaching hospital (2011- 2013) in Lusaka Zambia.

1.6 Specific Objectives

1.6.1 To determine the prevalence of pneumonia in sickle cell disease for under-five children who are referred to University Teaching Hospital.

1.6.2 To determine the haematological parameters which are mostly associated with pneumonia in sickle cell disease in under-five children

1.6.3 To establish a possible association between pneumonia and sickle cell disease in under-five children

1.6.4 To determine the outcomes of pneumonia in SCD for under-five children referred to University Teaching Hospital

CHAPTER 2

LITERATURE REVIEW

2.1 Global Burden of Pneumonia in SCD

Pneumonia and sickle cell disease are a major public health concern that has great impact on both individuals and society. The annual birth rate worldwide is over 200,000, with more than 90% of cases being in Africa (Davies et al., 2007). Mortality associated with these diseases is high despite knowledge of the pathophysiology (Lane et al., 1996, Bunn et al., 1997) and treatment of the various forms of crisis. Mortality from these diseases is highest in the first 5 years of life, with approximately 50% of deaths occurring in the second 6 months of life (Bainbridge et al., 1985, Thomas et al., 1982). Acute infections and severe anaemic sequestration are responsible for most of these deaths (Leikin et al., 1989, Rogers et al., 1978).

Approximately 30 million people worldwide have sickle cell disease (SCD) alone, making it one of the most common autosomal recessive disorders. It is estimated that 0.15% of African Americans in the U.S. are homozygous for SCD, and 8% are heterozygous weatherall et al., 2010. In the USA, it affects close to 100,000 people with 3000 affected newborns each year, while in the United Kingdom, it is estimated that 12,500 individuals have sickle cell disease with an annual birth rate of 300 affected newborns. Sickle Cell Disease is said to be the fastest growing serious genetic disorder in the UK and Western Europe (Subarna et al., 2014). Though the median survival is less than 50 years of age in the U.S., over 90% of those born with SCD live into their 20's (Platt et al 1994, Quinn et al., 2010), Although pain is the leading cause for health care utilization (Brousseau et al., 2010).

In a study of admission to hospital of 171 children with sickle cell disease, in South London, reviewed over a 20 year period, showed that 887 admissions occurred in 797 patients- years, the commonest cause of admission was painful vaso-occlusive crises followed by pulmonary disease, infection, anaemic episodes. Pneumococcal meningitis and acute splenic sequestration resulted in the most severe illness (Mutaza et al., 1981). In a study of SCD by Frances et al., Streptococcus pneumoniae was found to be the commonest cause of sepsis in young children less than two years of age. Out of a cohort of 600 patients 3.3% died. The commonest cause of death was infection. Eight of these deaths were due to infection caused

by streptococcus pneumoniae. Eighteen episodes of pneumococcal sepsis occurred before one year of life (Frances et al., 1989).

Acute chest syndrome (ACS), was first described by (Charache et al., 1979), is the second most common cause for hospitalization and a leading cause of death of those with SCD. It is estimated that nearly 50% of patients with SCD will have at least one episode of ACS in their lifetime (Castro et al., 1994, Paul., 2011). ACS occurs in 10–20% of those hospitalized with SCD, and in adults, usually 1–3 days after hospital admission. Death associated with ACS is four times higher in adults than in children (Castro et al., 1994). In addition, clinical manifestations of sickle cell disease vary over time, ranging from periods of wellness to the need for emergency care, suggesting hierarchical levels of disease complexity which require equally complex health care. Unfortunately, studies have shown that many professionals in primary health care are unaware of, or even ignore, sickle cell disease (Ludmila et al., 2011).

In a study by Hongeng et al, in a study of sepsis in sickle cell disease noted similarly, that streptococcus pneumoniae is the most common invasive infection among patients with sickle cell disease. He further observed that the risk of recurrent episodes of sepsis and subsequent death in those patients who have had a previous septic event is much higher. And, therefore, recommended that patients with sickle cell disease who have had pneumococcal sepsis should continue penicillin prophylaxis indefinitely (Hongeng et al., 1997). Further studies on the prevalence, molecular and clinical epidemiology of SCD may help predict disease severity and risk stratification of patients to determine whether to receive early intensive care or continued symptomatic care.Sickle cell disease (SCD) is one of the most important single gene disorders of human beings. In the United States, SCD affects about 72 000 people and 2 million are carriers (Wasil et al., 2011).

In a study to characterise recurrent infections in homozygous sickle cell disease, 214 episodes of invasive bacterial infections in 176 Jamaican patients with homozygous sickle cell disease were examined. Streptococcus pneumoniae occurred in 81 episodes, Salmonella species in 70, Haemophilus influenza type b in 30, Escherichia coli in 24 and Klebsiella species in nine. The cumulative incidence showed that S pneumoniae and H influenza occurred predominantly before five years and was uncommon thereafter (Wierenga et al., 2001).The acute painful crisis is the hallmark of the disease and the most common cause of hospitalization and treatment in the emergency department for SCD. It is associated with

inflammation, often culminating in serious complications and organ damage, such as ACS, multi-organ failure, and sudden death. It has been suggested that the physiologic events leading to ACS may start sometime during the early sequences of the painful episode, before the patient is hospitalized.

2.2 Burden of pneumonia in SCD in Africa

Acute chest syndrome (ACS) is the second most common cause of hospitalization and challenges infection in children (Leikin et al., 1989) as the leading cause of sickle cell-related mortality in children (Quinn et al., 2004).It is estimated that more than 300,000 babies with SCD are born annually; the majority of these are in sub-Saharan Africa, where access to medical care and public health strategies to decrease mortality and morbidity are not uniformly available (Diallo et al., 2014). This number is expected to increase to up to 400,000 individuals by 2050 (Piel et al., 2002).

In a study to describe the pattern of acute chest syndrome in sickle cell disease patients who attended the emergency department of a Lagos hospital, infections were found in 82% of all patients. The most common infections were pneumonia (35%) and septicaemia (32%) (Okuoghae et al., 1993).

The World Health Organization and United Nations have designated SCD as a global public health problem. One of the World Federation of Public Health Associations millennium development goals was targeted at reducing child mortality by two-thirds between 1990 and 2015 (Lomazzi et al., 2014). We believe that the high prevalence of undiagnosed non-communicable diseases, including SCD, contribute to excess mortality in children under five years. However, SCD patients are still hospitalized frequently and by the fifth decade of life, 48% of surviving patients have documented irreversible organ damage. In Africa, where comprehensive medical care is less available, death in early childhood is usual (Wasil et al., 2011). Sickle cell disease is the most important potentially devastating, recessively inherited condition. Acute chest syndrome (ACS) is one of the life-threatening vaso-occlusive complications seen in children with SCD. ACS is associated with high mortality rate, especially in sub-Saharan Africa and other low-income countries. Indeed, it is the second most common cause of hospitalization, and the leading cause of death, contributing to almost 25 % of SCD-related mortality.

Earlier studies conducted in the region of Congo and Nigeria also demonstrated the high frequency of Pneumococcal septicaemia in African children with sickle cell disease.
A retrospective study of 69 case reports of children with homozygous sickle cell anaemia hospitalized from 1964 through to 1985 at the Kinshasa University Paediatric Hospital highlighted this patients' high susceptibility to infection. Among causative organisms, the most prevalent were salmonellae (20 cases), Pneumococcal (15 cases), and Klebsiella (12 cases) (Omanga et al., 1989).

In 2006, the World Health Organization issued a report that specifically addressed SCD as a prevalent medical condition with clinical severity, contributing to the under-5 deaths on the African continent. This document identified an 'urgent need to develop models of care appropriate to the management of the disease in sub-Saharan Africa,' and recommended gradual introduction of services where feasible, emphasizing community education and partnership. The need for research and surveillance was also highlighted. Subsequently, the global burden has been quantified, with SCD accounting for 6.4% of the under-5 mortality across all of Africa. However, in certain countries with higher sickle allele frequencies and lower childhood mortality rates, such as Uganda, it is likely that SCD contributes to up to 15% of the under-5 mortality rate. Unfortunately, the vast majority of these cases are undiagnosed, and instead the causes of childhood mortality are attributed only to pneumonia or malaria, rather than the more accurate underlying SCD.

2.3 Burden of pneumonia in SCD in Zambia

In Zambia the sickle cell frequency ranges from 6% to 27% (Weatherall et al., 2001). Infections are the most common cause of mortality in children with sickle cell disease. Characteristically, the infections of sickle cell disease children are fulminant, without focus, and often fatal and typically caused by encapsulated streptococcus pneumoniae and to a lesser extent Haemophilus influenzae (Platt et al., 1994).

Children with SCD are at very high risk of invasive pneumococcal disease (300–500 times higher than the general population) because of loss of splenic filtrative function due to infarction (resulting in functional hyposplenism). Typical forms of pneumococcal disease in SCD include bacteraemia, sepsis, meningitis, and pulmonary infection. Hyposplenism is detectable by 3 months of age in Hb SS and Hb Sβ0, so it is necessary to begin prophylactic penicillin before then to prevent fatal pneumococcal sepsis (Quinn et al., 2014).

Infections are the most common cause of death among Zambian sickle cell disease children. A study by Athale et al observed that infections accounted for 29.84% of mortality among sickle cell patients (Athale et al., 1994).

In Zambia, infections are the most common cause of death among sickle cell disease patients aged between one and five years. Although infections have been noted to be the commonest cause of mortality in sickle cell disease patients less than five years of age, no studies in Zambia have been done to know the prevalence of pneumonia in SCD and the association of pneumonia and SCD (Athale et al., 1994).

CHAPTER 3

METHODOLOGY

3.1 Study Design

The study was cross-sectional using an existing dataset. The design was used in providing a snapshot of the pneumonia and SCD in Zambia with regard to the prevalence; haematological parameters affected most, pneumonia outcomes and association of pneumonia and sickle cell disease. This study was nested in the Pneumonia Aetiology Research for Child Health (PERCH) project which was a multi-country, standardized, and comprehensive evaluation of the aetiologic agents causing severe and very severe pneumonia among children in developing countries. The PERCH study has been designed as a case-control study that enrolled ~6000 patients hospitalized for severe or very severe pneumonia and ~6000 controls selected randomly from the community. The main reasons for this design are as follows: (1) the use of hospitalized patients, as opposed to those observed outside of facilities, is necessary to assure that we can safely collect a range of specimens from patients and that we gain the efficiency of testing only those with severe and very severe pneumonia; and (2) the inclusion of controls is important to guide the interpretation of results from the use of highly sensitive detection tests on upper respiratory tract specimens and to facilitate the identification of risk factors for pneumonia and/or specific etiologies. Although PERCH recognizes that pneumonia is an important illness in neonates and that important questions remain regarding the etiologies of serious pneumonia in this age group, it was considered sufficiently important and unique to require its own study, and thus PERCH focuses on children aged 1–59 months old. Using the same dataset that were collected had secondary variables such us sickle cell disease apart from pneumonia. My study focuses on prevalence of sickle cell disease in pneumonia, haematological parameters mostly associated with pneumonia and sickle cell disease, and any possible association between sickle cell disease and pneumonia.

The outcome variable was pneumonia. The exposure variables includes sickle cell disease, age, sex, outcomes (survival or death), and haematological parameters. Table 1 gives details of the study variables.

Table 1: Description of Study Variables

		Operational Definition	Scale of Measure	Indicator/ Test	Variable Type
Dependant Variable	Pneumonia	Infection of the Lungs	Nominal	Present or Absent	Binary
Independent Variables	Sickle cell disease	Autosome recessive disorder	Nominal	Negative or Positive	Binary
	Age	Length of time that a person has existed	Interval	Number of year	Continuous
	Sex	State of being Male or Female	Nominal	Male and Female	Binary
	Haematological parameters	Red cell indices, white blood cell, platelets, and differentials	Nominal	Test	Continuous
	Outcomes (survival or death)	Exit of hospital by being discharged or death	Nominal	Survival or death	Categorical

3.2 Study Site

The study site was the Department of Paediatrics at University Teaching Hospital, which is one of the tertiary hospitals located in the capital city, Lusaka, Zambia. The University Teaching Hospital receives referrals of pneumonia and sickle cell disease patients for further management from all part of Zambia. The University Teaching Hospital serves as the secondary and tertiary level of care. It has the bed capacity of more than 1500 beds. It is an academic centre and tertiary care facility with 425 paediatric inpatient beds.

3.3 Study Population

All children who were recruited for Pneumonia Aetiology Research for Child Health Project aged between 28 days and 59 months with pneumonia and sickle cell disease referred to the - University Teaching Hospital.

3.3.1 Inclusion Criteria

All children meeting the WHO criteria for severe abdominal, very severe pneumonia were screened for SCD 2011-2013 periods and aged 28 days to 59 months and were referred to paediatrics wing at the University Teaching Hospital.

3.3.2 Exclusion Criteria

All Children who resided outside the catchment areas and those that did not meet the WHO criteria for severe or very severe pneumonia were excluded from the study.

Figure 1: illustrates the algorithms of the study population from the point of referred, diagnosis up to the time of discharge.

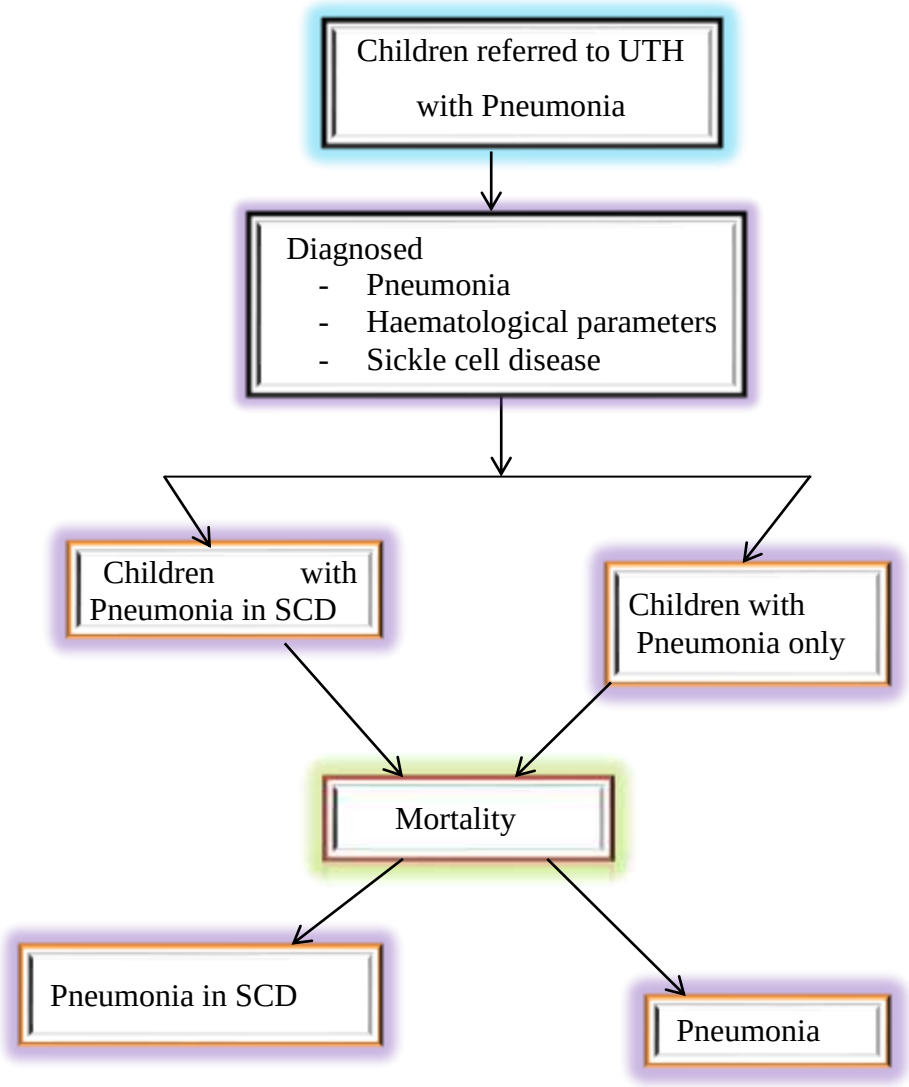

Figure 1: Schematic diagram of study population

3.4 Sampling and Sample Size

Complete enumeration was used for this research. All cases that were reported in 2011-2013 period for the pneumonia who were referred to the University Teaching Hospital were the study sample. The survey formulae were employed to get the minimum sample size as follows:

$$\mathbf{n} = \frac{Z^2\ \pi(1-\pi)}{\mathbf{e}^2}$$

$$\mathbf{n} = \frac{1.96^2\ 0.5(1-0.5)}{0.05^2}$$

$$\mathbf{n} = \frac{3.84 * 0.5(1-0.5)}{0.0025}$$

$$\mathbf{n} = \frac{0.9605}{0.0025} = 384.2 = 384$$

The sample size was **384**. This sample size was used as the minimum, and more cases were used than the calculated sample size.

3.5 Data Extraction

The study used secondary data which were obtained from University Teaching Hospital through Zambia Centre for Applied Health Research Development (ZCAHRD). The data were collected from children age one month to five years who had pneumonia cases. Sickle cell disease was secondary variable that were collected from the children who had pneumonia among other variables for the children who were referred to paediatric at the University Teaching Hospital. The data on the variables of interest for the period under review (i.e. 2011-2013) was extracted from the mother dataset using the Excel spread sheet and Epi Info™ version 6. The data were checked for accuracy and completeness. Participants with missing key information were removed from the dataset.

3.6 Statistical Analysis

3.6.1 Descriptive statistics

Statistical analysis was performed using STATA Version 13.0 (Stata Corporation, College Station, TX). Normally distributed data were summarised by the mean ± standard deviation (SD). The Continuous variables were tested for normality using the histogram or Shapiro-Wilk W-test to investigate normality graphically. The categorical variables were reported in frequencies and percentages.

3.6.2 Inferential statistics

Logistic regression analysis was performed using odds ratios (OR) with a 95% confidence interval (CI). For all tests, a *P*-value of <0.05 was considered to be statistically significant. Logistic regression was employed because the outcome variable pneumonia was binary. The univariate analyses model was fitted to determine the association between the pneumonia, and individual explanatory variables. The multivariate logistic regression was fitted to control for confounders while examining the association between pneumonia and sickle cell disease. The investigator led and backward stepwise regression model approach was used to select the best model. The best model was arrived at when the explanatory variables which had a p-value > 0.05 were removed from the model one by one until the p-value with the significant number remained in the model. In the backward stepwise regression the variables with p-values > 0.05 were removed automatic living variables of interest.

3.7 Dissemination

The findings of this study will be disseminated by presenting the summary of the final report to all stakeholders, and this are:

- Zambia centre for applied health research development (ZCAHRD)
- University Teaching Hospital management(UTH)
- University of Zambia libraries
- Public Health department(PHD**)**
- It will be published on the net

3.8 Ethical Considerations

Ethical approval with reference number 057-06-17 was obtained from University of Zambia Biomedical Research Ethic Committee (UNZABREC). The permission of use of the dataset from the custodian was sought before undertaking the study. The dataset of the sickle cell disease was kept confidential. The dataset was de-identified by the use of the codes developed by the principal investigator who ensured that all information collected could not be linked to the source hence preventing the identification of the participants. The information was kept on the excel sheet on a password secured computer and no unauthorized persons was able to access the information. However, ethical challenges that were encountered were minimal because the dataset that was used is secondary. The challenge that was encountered is lack of the complete dataset or missing vital information. The results of this study can be used to improve policies and enhance the future research as a manuscript will be submitted to a peer review journal for publication.

CHAPTER 4

RESULTS

This section provides an overview of the main findings presented in this study. A total number of under-five children admitted to University Teaching Hospital paediatric ward during the study period were approximately 3000.The overall total analysed in this study was 601.The findings of this study are presented in a chronological order starting with Schematic diagram of results for participants , Demographic and Clinical Characteristics of participants, followed by Basic characteristics of haematological parameters of participants and Haematological Parameters mostly associated with pneumonia and SCD.

The study recorded 84 cases of pneumonia in SCD during the study period, from a total of 601 under-five children being hospitalized with Pneumonia, hence an in-patient prevalence of 14 %. Their ages ranged from 28 days to 59 months years old, with a mean age (±SD) of 2.8 ± 1.4 months years old, the admitted under-five children with SCD and pneumonia during the study period, 45 (53.57%) were male, and 39 (46.43%) were female. Males were more represented than females with a sex ratio of 1.2/1.

Figure 2 is Schematic diagram of results for participants; Table 2a displays the Demographic and Clinical Characteristics of participants while Table 2b displays Basic characteristics of haematological parameters of participants. Table 3a and 3b are the univariate and multiple analyses of haematological parameters while Table 4 is the association of the sickle cell disease and pneumonia in under-five children. Figure 3 is the Receiver operating characteristic curve of sickle cell disease and pneumonia while Figure 4 is Mortality of under-five children during admission.

Figure 2: illustrates the overall findings of the study from the point of referral, diagnosis up to discharge.

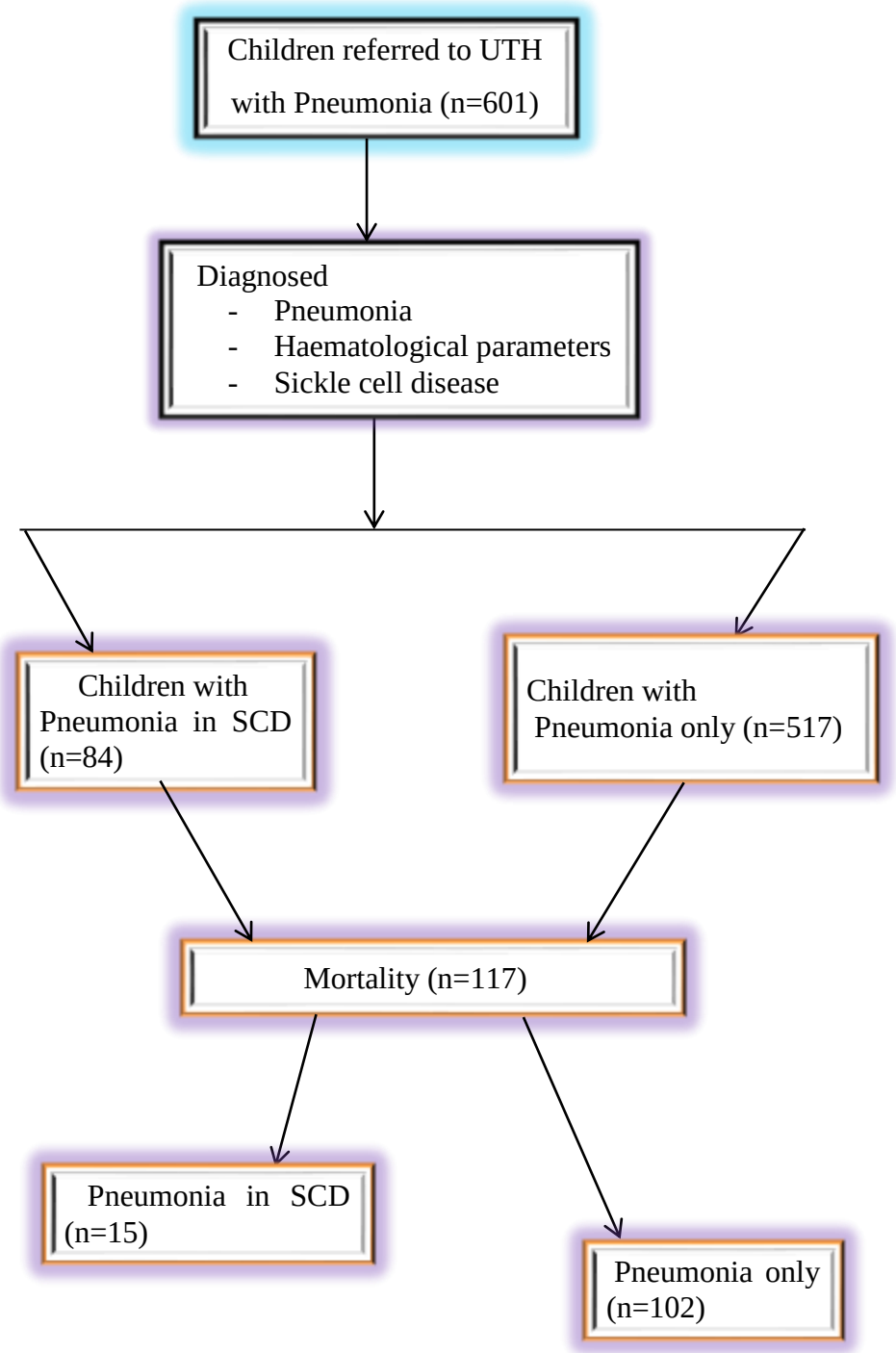

Figure 2: *Schematic diagram of results for participants*

Figure 2 above shows the flow diagram of the results for participants from the total admission of the under-five children up to the outcomes of the discharge status which are survival and death.

Table 2a: illustrates the demographic and clinical characteristics of all participants with pneumonia who met the inclusion criteria.

Table 2a: Demographic and Clinical Characteristics of participants

Characteristic	**Number (N = 601)**	**Percentage (%)**
Age		
Mean (SD)	2.8 (1.4)	
Pneumonia		
Severe	451	75
Very severe	150	25
Pneumonia and Sickle cell disease		
Positive	84	14
Negative	517	86
Sex		
Male	317	53
Female	284	47
Discharge status		
Survived	484	81
Died	117	20

Table 2a above shows the demographic and clinical characteristics of participants with pneumonia who met the inclusion criteria. The participants comprised of 317 males (53%) and 284 females (47%), while the mean age was 2.8 months old (S.D ± 1.4) with a range of 28 days to 59 months years old. The pneumonia cases were categorised as 451 severe pneumonia (75%) and 150 very severe pneumonia (25%).The discharge status was either survival or death after admission. The total under-five children who survived were 484 which are (80.5%) and those who died were 117(19.5%).

Table 2b: illustrates the Basic characteristics of haematological parameters of all participants with pneumonia in sickle cell disease.

Table 2b: Basic characteristics of haematological parameters of participants

Haematological parameter	Normal ranges	Mean	Standard Deviation
Haemoglobin	11.0 g/dL	9.67	± 1.57
Haematocrit	33 %	31.44	± 5.72
Mean cell volume	79.6 fL	77.24	± 10.69
Mean cell haemoglobin	26.7 Pg	23.91	± 4.26
Mean cell haemoglobin concentration	33.6 g/dL	30.69	± 2.39
Platelets	150×10^3 µL	387.27	± 182.09
White blood cells	6×10^3 µL	16.46	± 16.48
Red blood cells	4×10^6 µL	4.18	± 0.83
Neutrophils	38.51 %	46.66	± 18.95
Lymphocytes	18.21 %	41.43	± 17.03
Monocytes	4.41 %	9.63	± 5.26
Eosinophils	0.81 %	1.40	± 2.39
Basophils	0.11 %	0.41	± 0.58

The haematological parameters which were obtained in participants of pneumonia are shown in table 2b.The overall haematological parameters which are cardinal in pneumonia and SCD were 9.67 ±1.75 g/dL haemoglobin concentrations (Hb), 77.24 ±10.69 fL Mean cell volume (MCV), 23.91 ± 4.26 Pg Mean cell haemoglobin (MCH), 30.69 ± 2.39 g/dL Mean cell haemoglobin concentration (MCHC) and 4.18 ± 0.83 µL Red blood cells (RBCs).

The total number with pneumonia and sickle cell disease for the under-five in this study was 84, which gives the prevalence of 14%.

Table 3: illustrates the haematological parameters of all participants that are mostly associated with pneumonia in sickle cell disease

Table 3: Haematological Parameters mostly associated with pneumonia and SCD

	Univariate		Multivariate	
Pneumonia	**uOR (95% CI)**	**P-value**	**aOR (90% CI)**	**P-value**
Haemoglobin				
Normal	1		1	
Below normal	0.93 (0.85,1.02)	0.130	**1.59 (0.98,2.60)**	**0.060**
Red blood cells				
Normal	1		1	
Below normal	0.95 (0.77,1.18)	0.649	**0.30 (0.94,0.96)**	**0.043**
White blood cells				
Normal			**1**	
Below normal	1.01(0.99,1.03)	0.201	**1.02 (0.99,1.03)**	**0.079**
Mean cell haemoglobin				
Normal	1		1	
Below normal	0.97 (0.93,1.02)	0.195	**0.79(0.65,0.97)**	**0.022**
Monocytes				
Normal			**1**	
Below normal	1.02(0.99,1.05)	0.232	**1.03(0.99,1.07)**	**0.051**

uOR [unadjusted odds ratio]
aOR [adjusted odds ratio]
95% CI [Confidence interval]
P-value were derived from chi square

HB normal is 11 g/dL
RBCs normal is 4.18×10^{6}µL
WBCs normal is 6×10^{3}µL
MCH normal is 26.7 Pg
MON normal is 4.41%

Table 3 above is the logistic regression model in which univariate and multivariate logistic regression analyses of the haematological parameters were performed. The univariate shows that all cells were not statistically significant at p-value 0.05. The multiple logistic regression was performed by the investigator-led stepwise regression with p-value of 0.1 and 90% Confidence interval, the following cells were statistically significant, haemoglobin (Hb), red blood cells (RBCs) white blood cells (WBCs), mean cell haemoglobin (MCH) and monocytes (MON).

Table 4: illustrates the association of Pneumonia and Sickle cell disease in under-five children.

Table 4: The association of Pneumonia and Sickle cell disease in under-five children

Pneumonia	OR [95% CI]	p-value
Sickle cell disease	0.73(0.45,1.29)	0.283

Table 4 shows the association of the pneumonia and sickle cell disease. The pneumonia is not associated with the sickle cell disease according to the p-value obtained 0.283.

Figure 3: illustrates the receiver operating characteristic curve of sickle cell disease and pneumonia which measures the validity.

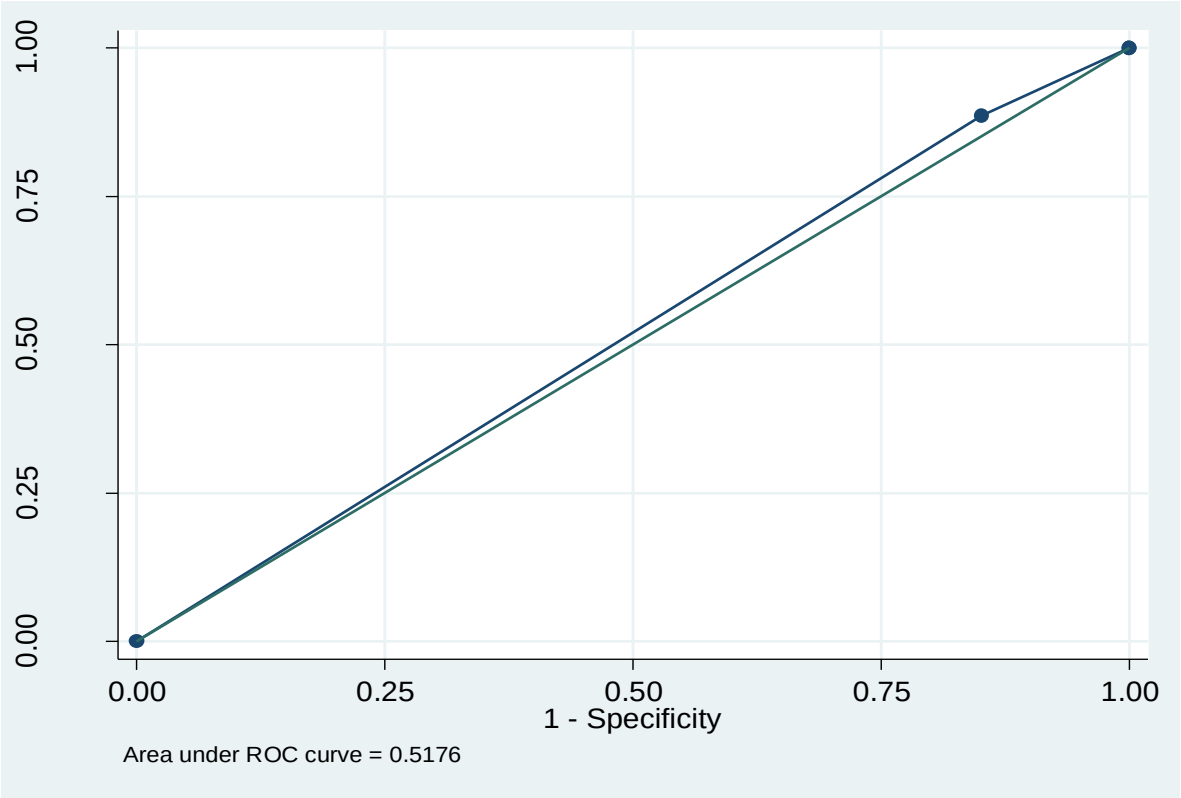

Figure 3: The Receiver operating characteristic curve of sickle cell disease and pneumonia

We also used the receiver operating characteristics (ROC) curve which measures validity. The receiver operating curve suggested that classification was due to chance. This is because the receiver operating curve value was close to 0.5 than to 1

Figure 4: illustrates the outcomes of pneumonia in sickle cell disease and pneumonia which is mortality of under-five during admission.

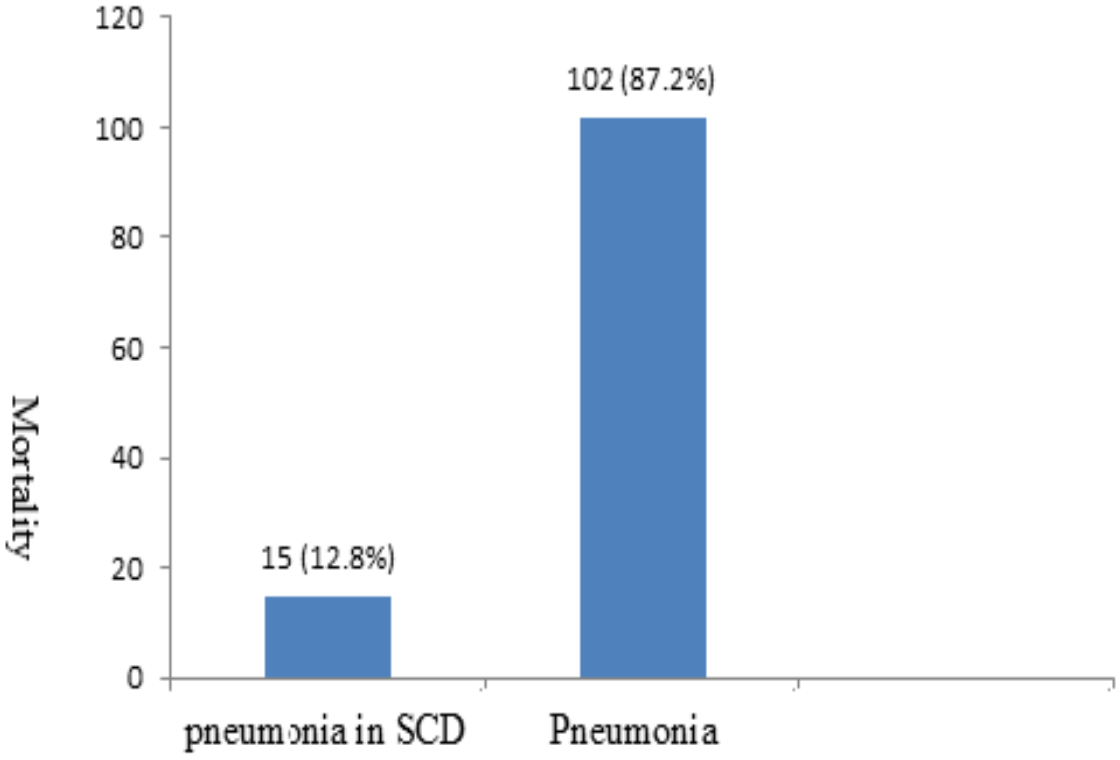

Figure 4: Mortality of under-five children during admission

Figure 4 shows the outcomes of pneumonia in SCD and pneumonia which is mortality of under-five during admission. Total deaths either associated with pneumonia in SCD or pneumonia was 117 (19.5%). The children who died with factors only associated with pneumonia in SCD were 15(12.8%) while 102(87.2%) died with factors associated with pneumonia only.

CHAPTER 5

DISCUSSION

Thus, this study aimed at determining prevalence, haematological parameters which are mostly associated with pneumonia in sickle cell disease, and the outcomes of pneumonia in sickle cell disease. Participants' mean age was 2.8 months old (S.D ± 1.4) with a range of 28 days to 59 months old. The study revealed that pneumonia in SCD accounted for 14 % of all under-five children admitted during the study period. This proportion is comparable to the studies done by (Bertholdt et al., 2012), and higher than the studies done by (Elenga et al., 2014). However, our prevalence of pneumonia in SCD is within the 10–20 % rate of hospital admissions reported by Miller and Gladwin in their review (Miller et al., 2012). On the contrary, our findings are higher than what were observed by (Pule et al., 2014) in the USA and Europe, who together account for less than 8% of the global disease burden of pneumonia in sickle cell disease. This is a high prevalence for under-five children with pneumonia in sickle cell disease. The study findings are not consistence with the study conducted by (Powars et al., 1975) where they obtained the prevalence of 10%. The findings from the study showed that the frequency of pneumonia in SCD among males was high compared to that of the females but the study by (Olagunju et al., 2017) revealed more females as opposed to males. Basically the prevalence of pneumonia in sickle cell disease in Zambia is not known, however, this prevalence obtained in this study will save as the baseline for other studies.

The higher burden of pneumonia in sickle cell disease results in the more children being hospitalized and some of those who are in school may leave school due to in and out of hospitals, most likely because of their illness. (Shapiro et al., 1995) found that, approximately half of school absences for children are associated with sickle cell disease-related pain. Other causes of school absences include minor infections, clinic visits, and other medical problems associated with sickle cell disease. In addition, families may perceive their children as vulnerable and keep them out of school for problems that would not interfere with school attendance for most children. Sickle cell disease -related pain and illness also have been shown to affect the psychosocial function and thus the school attendance of these children. Pneumonia in SCD includes the lifelong challenges of managing the chronic illness while accessing and navigating the health care system. The burdens of the diseases can affect all

aspects of the lives of individuals with SCD to include physiological, psychological, and social well-being. **(**Coretta et al., 2011)

The study also speculated a significant increase in the proportion of under-five children with pneumonia in sickle cell disease, suggesting a high prevalence of disease among under-five children in the general population who are undiagnosed.

In this study, the haematological parameters of patients with pneumonia in SCD constituted of full blood count and differentials. The study revealed that haemoglobin, red blood cells, white blood cells, monocytes and mean cell haemoglobin are cells mostly associated with pneumonia in SCD. In the study carried out by (Sanjeev et al., 2012), their findings on cells that are associated with pneumonia in sickle cell disease were similar to ours, and they revealed that haemoglobin (Hb), red blood cells (RBCs) Mean cell haemoglobin (MCH) and Mean cell haemoglobin concentration (MCHC) are mostly associated with the diseases. These cells are reduced in sickle cell disease due to increase in cells haemolysis in blood vessels while MCV is high in sickle cell disease patients because of the increasing need of erythropoiesis due to chronic haemolysis leading to macrocytosis. The study revealed that under-five children whose haemoglobin were below normal presented with anaemia due to low haemoglobin. These children had 59% chance of having anaemia as opposed to the children with normal haemoglobin, while the under-five children whose red blood cells and its indices mini cell haemoglobin count where below 70% and 21% in respect of the normal values. The white blood cells and monocytes increased in these children due to the presence of infections.

The red blood cells contain a substance called haemoglobin, which combine with the air (oxygen) in the lungs, carry round the body to all the body parts to keep the body tissues and organs alive. Haemoglobin gives blood its red colour when it contains oxygen. These haemoglobin molecules stay freely flowing in the red blood cell. However, when sickled red blood cells, break down prematurely, it leads to anaemia. Anaemia can cause shortness of breath, fatigue, and delayed growth and development in children. The rapid breakdown of red blood cells may also cause yellowing of the eyes and skin, which are signs of jaundice. Painful episodes can occur when sickled red blood cells, which are stiff and inflexible, get stuck in small blood vessels. These episodes deprive tissues and organs of oxygen-rich blood and can lead to organ damage, especially in the lungs, kidneys, spleen, and brain.

Our study revealed no evidence of association between sickle cell disease and pneumonia but a lot of studies have been done between pneumonia and malaria and as well as Human immunodeficiency virus (HIV). However, no evidence in literature that suggests any association apart from both diseases being susceptible to infections such as *Streptococcus pneumoniae*. These diseases occur independently since the sickle cell disease is due to autosomal recessive disorder and they are susceptible to infections with encapsulated organisms. Pneumonia can be caused by a myriad of microorganisms; clinical suspicion of a particular offending agent is derived from clues obtained during the history and physical examination. While any microorganism can lead to pneumonia, specific bacterial, viral, fungal, and mycobacterial infections are most common in previously healthy children. Pneumonia and other lower respiratory infections are the leading cause of death worldwide.
Further the study revealed that an increase in severe pneumonia, increased the odds of sickle cell disease.When the study compared the pneumonia types, the study revealed that children who had severe pneumonia were at higher risk of having reduced the haematological profiles as compared to very severe pneumonia, which decreased the odds of sickle cell disease in under-five children.

The study used the receiver operating characteristics curve which is designed to measure the validity. The receiver operating characteristics curve measured the validity. The receiver operating curve suggests that classification is due to chance. This is because of the receiver operating curve value which is close to 0.5 than to 1. Meaning the chance of association between sickle cell disease and pneumonia is reduced.

The study further compared the mortality between the pneumonia in SCD and pneumonia during the period of study. The mortality of under-five with pneumonia in SCD was 12.8% while pneumonia were 87.2%.More Children are dying from factors that are related to pneumonia as opposed to factors associated with pneumonia in sickle cell disease. The lower in mortality of pneumonia in SCD when compared to pneumonia could be due to the dataset which was mainly collected for pneumonia aetiology study.

The limitation of this study may not be representative of the wider population. The study design used in this study has the limitation of not ascertaining the causal inferences. However, the information that has been generated is useful to inform policy addressing this very important public health matter. In our study the data were limited to a single tertiary care

which is the University Teaching Hospital (UTH). This may limit the ability to generalize our findings to a larger paediatric population with pneumonia in SCD.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

In summary, we have seen a recent increase in the frequency of pneumonia in sickle cell disease. Pneumonia continues to be a serious and sometimes fatal complication in SCD. These findings should drive continued efforts to influence treatment algorithms and diagnostic approaches in order to reduce the morbidity and mortality of the pneumonia in SCD. However, this study achieved its set objectives, by determining the high prevalence of pneumonia in SCD which causes the high rate of morbidity and mortality. The study also revealed haemoglobin, red blood cells, white blood cells, mean cell haemoglobin and monocytes as cells that are mostly associated with pneumonia in SCD. The study showed that there is no evidence of association between pneumonia and sickle cell disease and furthermore, the study compared mortality of pneumonia and pneumonia in SCD in which pneumonia only had a higher mortality than pneumonia in SCD. This highlights the need for better diagnostic services, wider pneumonia in SCD screening and clinical audits to improve outcomes in order to achieve further reductions in under-five children mortality and maintain the gains.

6.2 Recommendations

Prevalence of pneumonia in sickle cell disease in Lusaka is high hence awareness, surveillance or screening of the disease in under-five children should be intensified in order to reduce the burden of the disease. All patients with pneumonia need to be vaccinated with pneumococcal vaccine (PCV). The National wide screening of pneumonia and SCD are required in order to reduce the morbidity and mortality in under-five children. The government through the Ministry of Health and other partners need to formulate policies towards the reduction of pneumonia in sickle cell disease in Zambia. The haematological parameters such as haemoglobin, red blood cells, white blood cells, mean cell haemoglobin and monocytes should be considered when dealing with pneumonia in SCD patients.

REFERENCES

Gill, F.M, et al.(1995*).Clinical events in the first decade in a cohort of infants with sickle cell disease,* Cooperative Study of Sickle Cell Disease. Blood 1995; 86:776–783 [PubMed]

Powars, D. Weidman, J.A. Odom-Maryon. Niland, J.C and Johnson, C. (2015) .Sickle cell chronic lung disease: *prior morbidity and the risk of pulmonary failure*. Medicine (Baltimore) 1988; 67:66–76 [PubMed]

Shilpa, J. Nitya, B and Lakshmanan, K. (2017) *Acute Chest Syndrome in Children with Sickle Cell Disease* [Published online 2017 Dec 1. doi: 10.1089/ped.2017.0814PMCID:] PMC5733742 PMID: 29279787

Makani, J. Ofori-Acquah, S. F. O. Nnodu,A. Wonkam. and Ohene-Frempong, K. (2013). Sickle Cell Disease: *New Opportunities and Challenges in Africa*. ScientificWorldJournal. 2013; 2013: 193252. [Published online 2013 Sep 19. doi: 10.1155/2013/193252 PMCID: PMC3988892]

Maitre, B. Habibi, A. Roudot-Thoraval, F. (2000) *Acute chest syndrome in adults with sickle cell disease: therapeutic approach, outcome, and results of BAL in a monocentric series of 107 episodes*. [Chest. 2000; 117: 1386–1392].

Nansseu,J.R.N,Yanda,A.N.A,Chelo,D,Tatah,S.A,Awa,H.D.M,Seungue,Jand Koki, P.O.N (2015) *The Acute Chest Syndrome in Cameroonian children living with sickle cell disease:* BMC Paediatrics (2015) 15:131 DOI 10.1186/s12887-015-0454-0.

Davies, S.C. (2007). *Haemoglobinopathies, Paediatrics and child health*.2007; 17(8):311–6.

Lane, P.A. (1996). *Sickle cell disease.* Paediatr Clin North Am. 1996; 43(3):639–64. [PubMed]

Bunn, F.H (1997) *Pathogenesis and treatment of sickle cell disease* N Engl J Med. 1997; 337(11):762–9. [PubMed]

Bainbridge, R. Higgs, D.R .Maude, G.H and Sergeant, G.R. (1985).*Clinical presentation of homozygous sickle cell disease* [J Pediatr. 1985; 106(6):881–5. [PubMed]

Leikin, S.J, Gallagher, D and Kinney, TR, (1989) *Mortality in children and adolescents with sickle cell disease.* Paediatrics. 1989; 84(3):500–8. [PubMed]

Thomas, A.N, Pattison, C and Sergeant, G.R.(1982) *Causes of death in sickle cell disease in Jamaica.* Br Med J. 1982; 285(6342):633–5. [PMC free article] [PubMed]

Rogers, D.W, Clark, J.M, and Cupidore, L. (1978) *Early deaths in Jamaican children with sickle cell disease*. Br Med J. 1978; 1 (6126):1515–6. [PMC free article] [PubMed]

Weatherall, D. J., 2010, "The Inherited Diseases of Hemoglobin are an Emerging Global Health Burden," Blood, 115(22), pp. 4331–4336.

Subarna, C. Thomas, N. W. (2015). Sickle cell disease: *A neglected chronic disease of increasing global health importance*.[Published online 2014 Sep 19]. Arch Dis Child 2015. Jan; 100(1): 48–53.. doi: 10.1136/archdischild-2013-303773 PMCID: PMCID: PMC4285890.

Platt, O. S. Brambilla, D. J. Rosse, W. F. Milner, P. F. Castro, O., Steinberg, M. H., and Klug, P. P., (1994) "*Mortality in Sickle Cell Disease—Life Expectancy and Risk Factors for Early Death*," N. Engl. J. Med., 330(23), pp. 1639–1644.

Quinn, C. T., Rogers, Z. R., McCavit, T. L., and Buchanan, G. R., (2010) "*Improved Survival of Children and Adolescents with Sickle Cell Disease*," Blood, 115(17), pp. 3447–3452.

Brousseau, D. C., Owens, P. L., Mosso, A. L., Panepinto, J. A., and Steiner, C.A., (2010) "*Acute Care Utilization and Rehospitalizations for Sickle Cell Disease*," JAMA, 303(13), pp. 1288–1294.

Frances, M.G. Audrey, B. Dianne, G (1981) *Newborn experience in the cooperative study of sickle cell disease.* Paediatrics.1989. Supplement 829

Mutaza, L.N. Stroud, C.E. Davis, L.R. Cooper, D.J. (1981). *Admission to hospital of children with sickle cell anaemia- a study in south London;* British Medical Journal 1981 Mar 28; 282 (6269); 1048-51.

Charache, S., Scott, J. C., and Charache, P., (1979), "*Acute Chest Syndrome in Adults With Sickle Cell Anaemia: Microbiology, Treatment, and Prevention*," Arch. Intern. Med., 139(1), pp. 67–69.

Castro, O., Brambilla, D. J., Thorington, B., Reindorf, C. A., Scott, R. B., Gillette,P., Vera, J. C., and Levy, P. S., (1994), "*The Acute Chest Syndrome in Sickle Cell Disease: Incidence and Risk Factors*. The Cooperative Study of Sickle Cell Disease," Blood, 84(2), pp. 643–649.

Paul, R. N., Castro, O. L., Aggarwal, A., and Oneal, P. A., (2011), "*Acute Chest Syndrome: Sickle Cell Disease*," Eur. J. Haematol., 87(3), pp. 191–207.

Ludmila, M.X. G. Magda, M.V. Tatiana, C. R. Thiago, L.A. B. and Antônio, P C. (2011). *Knowledge of family health program practitioners in Brazil about sickle cell disease: a descriptive, Cross-sectional study*.[published online 2011 August 19] http://www.biomedcentral.com/1471-2296/12/89.Accepted:19 August 2011.

Hongeng, S. William, J.A. and Harris, S. (1997). *Recurrent streptococcus pneumonia sepsis in children with sickle cell disease* [Journal of paediatrics 1997; 130(5):814-6]

Wasil, J..(2011). *Epidemiology of sickle cell disease in Saudi Arabia*. Ann Saudi Med. 2011 May-Jun; 31(3): 289–293].

Wierenga, K.J.J. (2001). *Significance of fever in Jamaican patients with homozygous sickle cell disease* [Archives of diseases of childhood 2001; 84; 156 – 159]

Quinn, C.T. Rogers, Z.R and Buchanan, C.R (2004) *Survival of children with sickle cell disease*. Blood. 2004; 103(11):4023-4027. **PubMed** | **Google Scholar**

Diallo, D. and Tchernia, G.(2002).*Sickle cell disease in Afric*a [Curr Opin Hematol 2002; 9:111].

Piel, F.B, Patil, A.P, Howes, R. E and Nyangiri, O.A (2013) Global epidemiology of sickle haemoglobin in neonates: *a contemporary geostatistical model-based map and population estimates*. [Lancet. 2013; 381(9861):142-151. **PubMed** | **Google Scholar]**

Okuoghae, H.O. (1993) *Pattern of bacteraemia in febrile children with sickle cell anaemia*. [Annals of Tropical Paediatrics. 1993; 13 (1) 55-64;]

Lomazzi M, Borisch B, Laaser U. The Millennium Development Goals: experiences, achievements and what's next. Glob Health Action 2014; 7:23695.

Omanga, U. (1989). *Bacterial septicaemia in children with homozygous sickle cell anaemia* Analysis of 69 cases; [Annals of paediatrics (Paris). 1989 May; 36 (5); 315-8;

Quinn, C. T. (2014). *Sickle Cell Disease in Childhood*.[Updated on December,2013]:pediatr Clin North Am.2013 December;60(6):1363-1381.doi:10.1016/j.pcl.2013.09,006.

Chintu,C. and Athale (1994). *Clinical analysis of mortality in hospitalized Zambian children with sickle cell anaemia*. [published on East Afr Med J. 1994 Jun; 71(6):388-91].

Beauvais, P. (1982) *Sickle cell anaemia and functional asplenia* (author's transl) [Arch Fr Pediatr 1982; 39:141–4]

Battersby, A.J. Knox-Macaulay, H.H. Carrol, E.D. (2010) *Susceptibility to invasive bacterial infections in children with sickle cell disease.* Pediatr Blood Cancer 2010; 55:401–6.

Overturf, G.D. Powars, D. Baraff, L.J. (1977) *Bacterial meningitis and septicaemia in sickle cell disease*.[Am J Dis Child 1977; 131:784–7.]

Powars, D.R. (1975). *Natural history of sickle cell disease—the first ten years* [Semin Hematol 1975; 12:267-85]

Barrett-Connor, E. (1971) *Bacterial infection and sickle cell anaemia, An analysis of 250 infections inn 166 patients and a review of the literature* [Medicine (Baltimore) 1971;50:97-112.]

Pearson, H.A. Spencer, R.P. Cornelius, E.A. (1969) *Functional asplenia in sickle-cell anaemia.* [N Engl J Med 1969; 281:923-6.]

Grosse, S.D. Odame, I. Atrash, H.K. Amendah, D.D. Piel, F.B. (2011). Sickle cell disease in Africa: *A neglected cause of early childhood mortality*. [Am J Prev Med 41: S398–405].

Scott, D. G. Isaac, O. Hani, K. A. Djesika, D. A. Frédéric, B. P. and Thomas, N. W. (2011). Sickle Cell Disease in Africa. Sickle Cell Disease. *New Opportunities and Challenges in Africa* .[Scientific World Journal., Published online 2013 Sep 19. doi: 10.1155/2013/193252].

Orin, S. L. Katherine, L. O. Maria, D. David, R. M. Daniel, R. F. Andrea, N. D. Amanda, J. D. Henry, C. B. W. Abdullah ,B. Stephen, R. C. Howie,K. L. Kotloff, S. Madhi, A .Susan, A. Maloney,. Samba, S. (2012). *The Pneumonia Etiology Research for Child Health Project*: *A 21st Century Childhood Pneumonia Etiology Study*. [PMCID: PMC3988892].

Hamideh, D and Alvarez, O (2013) *Sickle cell disease related mortality in the United States (1999–2009). Pediatr Blood Cancer* 2013; 60:1482–1486

Sylvester, K.P. Patey, R.A. Milligan, P (2004) *Impact of acute chest syndrome on lung function of children with sickle cell disease*. *J Pediatr* 2006; 149:17–22

Bertholdt, S. Lê, P.Q. Heijmans, C. Huybrechts, S. Dedeken, L. Devalck, C (2012) *Respiratory complications of sickle cell anaemia in children*: the acute chest syndrome. [Article in French, Rev Med Brux. 2012;33(3):138–44.]

Elenga, N. Cuadro, E. Martin, E. Cohen-Addad, N. and Basset, T (2014) *Associated factors of acute chest syndrome in children with sickle cell disease in French Guiana*. [Int J Pediatr. 2014; 2014:213681.]

Miller, A.C. Gladwin, M.T.(2012) *Pulmonary complications of sickle cell disease*. [Am J Respir Crit Care Med. 2012; 185(11):1154–65.]

Gift, P. and Ambroise, W. (2014). Treatment for sickle cell disease in Africa: *should we invest in haematopoietic stem cell transplantation*. [Pan African Medical Journal.2014;18:46 doi:10.11604/pamj.2014.18.46.3923].

Shapiro, B. S, Dinges, D. F and Orne, E.C.(1995) *"Home management of sickle cell-related pain in children and adolescents: natural history and impact on school attendance*," *Pain*, vol. 61, no. 1, pp. 139–144, 1995.

Coretta, M, Jenerette, and Cheryl Brewer (2011) *Health-Related Stigma in Young Adults With Sickle Cell Disease* **J Natl Med Assoc. 2010 November; 102(11): 1050–1055.**

Powars (1975) Natural *history of sickle cell disease--the first ten years* [Semin Hematol. 1975; 12(3):267–285. [PubMed: 237323]

Barrett-Connor, E. (1971) *Bacterial infection and sickle cell anaemia: An analysis of 250 infections in 166 patients and a review of the literature:* [*Medicine*, vol. 50, no. 2, pp. 97–112].

Piel, F.B, Patil, A.P, Howes, R.E and Nyangiri, O.A (2013) Global epidemiology of sickle haemoglobin in neonates: *a contemporary geostatistical model-based map and population estimates*. Lancet. 2013; 381(9861):142-151. **PubMed** | **Google Scholar**

Grosse, S.D, Odame, I, Atrash, H.K and Amendah, D.D, (2011) Sickle Cell Disease in Africa: *A neglected cause of early childhood mortality.* Am J Prev Med. 2011; 41(6):398-405. **PubMed** | **Google Scholar**

APPENDIX